High-Flow Nasal Cannula Oxygen Therapy for the Treatment of Acute Hypoxemic Respiratory Failure for COVID-19

Rapid Review

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1. CONTEXT AND POLICY ISSUES

In early 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing novel coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 160 countries and regions with at least 5,594,175 cases and 350,547 deaths worldwide as of 27 May 2020 (Dong, Du & Gardner, 2020). In the Philippines, there have been over 432,925 COVID-19 cases with 8,418 deaths as of 1 December 2020 (Department of Health, 2020a). To date, there is no known treatment for SARS-CoV-2 (Dong, Du & Gardner, 2020).

The spectrum of COVID-19 symptomatic infection ranges from mild to critical, with most infections considered not severe. However, some patients with initially non-severe symptoms may progress over the course of a week. One of the several complications of COVID-19 include respiratory failure, more specifically acute respiratory distress syndrome (ARDS). ARDS is a major complication in patients with severe coronavirus disease and can manifest shortly after the onset of dyspnea or difficulty in breathing (McIntosh, 2020). Among those who are critically ill, profound acute hypoxemic respiratory failure (AHRF) from ARDS is a common finding (Anesi, 2020). Acute hypoxemic respiratory failure is a type of severe arterial hypoxemia that can be caused by intrapulmonary shunting of blood resulting from airspace filling or collapse. Clinical manifestations include dyspnea and tachypnea (rapid breathing) and diagnosis is performed by arterial blood gas (ABG) measurement and chest x-ray (Patel, 2020).

As scientists draw near to discovering curative or preventive treatments for COVID-19, various respiratory supportive treatments are currently the common management pathway of COVID-19 with ARDS. *In the Health Professionals Alliance Against COVID-19 (HPAAC)'s Unified COVID-19 Algorithm issued last November 7, 2020,* an adult patient with COVID pneumonia with respiratory symptoms or distress can be started with oxygen support therapy. For the purposes of this review, it is important to define the terms *oxygenation* and *ventilation*. Oxygenation refers to the delivery of oxygen to the tissues to maintain cellular activity, while ventilation refers to the act of normal, spontaneous breathing (i.e., inhalation and exhalation) (Ausmed, 2020). Hypoxemia results from inadequate supply of oxygen due to various mechanisms, one of which is hypoventilation (Theodore, 2020). Hypoxemia can be primarily corrected by provision of conventional oxygen therapy (COT) (e.g., oxygen face mask, nasal prongs or cannulas). In the event where the patient remains hypoxemic, ventilatory support may be used (Shelly & Nightingale, 1999). Ventilatory support may be classified in terms of invasiveness of the medical equipment (i.e., delivery of oxygen involves insertion of devices into the human body):

- Invasive ventilation – delivery of positive pressure to the lungs via an endotracheal or tracheostomy tube
- Non-invasive ventilation (NIV) – delivered through an alternative interface, such as oxygen hood or face mask (Hyzy & McSparron, 2020)

According to Patel, Kress & Hall (2020), there is currently an ongoing debate regarding the issue on whether to intubate early or not, and if otherwise, which type of non-invasive respiratory support (HFNC or other NIVs) is the most efficacious for COVID-19 patients with AHRF. HFNC, bi-level positive airway pressure (BiPAP), and continuous positive airway pressure (CPAP) are collectively known as NIVs. BiPAP and CPAP are sub-classified as non-invasive positive pressure ventilators (NPPV or NIPPV), owing to their abilities to provide positive pressure during oxygen supplementation.

Ventilation techniques (both invasive and non-invasive) have always been known to have both risks and benefits. Their use is accompanied with limitations, including mobility restrictions for the patient (i.e., being physically attached to a ventilator), and creation of mechanical stress and cause of strain

on lung tissue. This can lead to ventilator-induced lung injury, compounding the underlying lung condition that precipitated the initial respiratory failure (Patel, Kress & Hall, 2020). Over the years, there have been many protective measures and strategies that limit ventilator-induced lung injury; however, it still remains a concern for patients undergoing intubation and mechanical ventilation. Focusing on invasive ventilations, a study by Richardson, Hirsch & Narasimhan (2020) among patients hospitalized with COVID-19 in the city of New York suggested high mortality for patients with COVID-19–associated respiratory failure who received invasive mechanical ventilatory support, raising the concern that these patients may be particularly vulnerable to ventilator-induced lung injury. Further, patients under invasive ventilators may be at risk of acquiring ventilator-associated bacterial pneumonia (VAP) (Póvoa et al., 2020), a secondary bacterial infection that can complicate the management of COVID-19 patients.

NIV techniques in general have substantially reduced the need for invasive mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema (Patel, Kress & Hall, 2020). For patients with acute *hypercapnic* respiratory failure (i.e., failure to eliminate excess carbon dioxide in the body but close to normal oxygen levels), the use of NIV is associated with a marked reduction in the need for endotracheal intubation, a decrease in complication rate, a reduced duration of hospital stay and a substantial reduction in hospital mortality (Brochard, 2003). An example of a non-invasive ventilation (NIV) is high-flow nasal cannula (HFNC). HFNC is a type of non-invasive ventilation equipment that involves the use of positive pressure environment to reduce nasopharyngeal and nasal resistance for improved ventilation and oxygenation. HFNC makes use of high flow rates to support the patient in ventilating by delivering volumes of air which displaces excess CO_2 with increased O_2. This mechanism results to a greater oxygen diffusion gradient and improved patient oxygenation (Sharma, et al., 2020). According to Drake (2018), a normal physiologic inspiratory flow rate during quiet breathing is 30 L/min. Conventional oxygen therapy (COT) provides flow rates at a maximum of 15 L/min, while HFNCs can provide up to 60 L/min flow rate; thus, HFNC can better provide oxygen supplementation in patients with acute respiratory failure requiring higher inspiratory flow. In a comparison by Sakhpara (2019) of HFNC versus other NIVs, HFNC was more advantageous because it:(1) may wash out the anatomic dead space and reduce the work of breathing, and (2) facilitates more effective and better communication with the patient (versus bi-level positive airway pressure, or BiPAP). Furthermore, according to Drake (2018), the increasing use of HFNC is attributed to its superior clinical efficacy compared with conventional low-flow oxygen supplementation and other non-invasive ventilation (e.g., non-invasive positive pressure ventilation or NIPPV) in AHRF as well as its physiologic benefits when compared with conventional low-flow oxygenation.

According to the PhilHealth Circular no. 2020-0009 (dated April 8, 2020) with the subject "*Benefit packages for inpatient care of probable and confirmed COVID-19 developing severe illness/ outcomes*," PhilHealth will cover (through its COVID-19 benefit package) additional necessary medical services needed by patients with critical pneumonia who develop or with impending illness, which include, but not limited to the following: ARDS, septic shock, requiring invasive ventilation, requiring extracorporeal membrane oxygenation (ECMO), or requiring renal replacement therapy. In addition, the Department of Health, through its press release dated September 9, 2020, allocated PHP 4.5 billion of its Bayanihan 2 We Recover As One Act fund for purchase of various medical equipment, which includes 200 units of HFNC, among others.

However, defining the role of these oxygenation and ventilation techniques in AHRF from lung injury has remained elusive (Patel, Kress & Hall, 2020), and the level of success of NIV is more variable (Brochard, 2003). Further, COVID-19 spreads through respiratory droplets and fomites – raising a concern that airborne transmission may occur during procedures that generate aerosols. The use of high flow rates in HFNC may cause aerosolization of infectious particles (Agarwal et al., 2020a). As

PhilHealth constantly reviews its COVID-19 benefit package, it has sought the Health Technology Assessment Council's recommendation on the continued use of HFNC for COVID-19 patients. As such, this rapid review examines the existing evidence on the use of HFNC for AHRF in COVID-19 patients.

2. POLICY AND RESEARCH QUESTIONS

POLICY QUESTION

Should high-flow nasal cannula (HFNC) oxygen therapy for the treatment of acute hypoxemic respiratory failure (AHRF) among COVID-19 patients be recommended for expansion or disinvestment by DOH and PhilHealth?

RESEARCH QUESTIONS

1. **Clinical Performance**

   Clinical effectiveness

   Among COVID-19 patients, is HFNC oxygen therapy more effective than other NIVs in treating acute hypoxemic respiratory failure based on the following outcomes?

   - Mortality
   - Failure of respiratory support (escalation to invasive ventilation)
   - Length of hospital stay
   - Length of ICU stay

   Clinical safety

   Among COVID-19 patients, is HFNC oxygen therapy safer than other NIVs in treating acute hypoxemic respiratory failure based on risk of aerosolization of respiratory droplets?

   Clinical guidelines and evidence synthesis on use of HFNC

   - *Which country/countries have implemented HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?*
   - *What is the current position/ recommendation of HTA agencies regarding the use of HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?*

2. **Resource Requirements and Associated Costs**
   What are the resource requirements and associated costs on the use of HFNC or other NIVs in treating COVID-19 patients with acute hypoxemic respiratory failure?

3. **Ethical and Social Impact Assessment**
   What are the ethical and social issues on the use of HFNC among COVID-19 patients with acute hypoxemic respiratory failure?

3. KEY FINDINGS

This rapid review intended to synthesize the most recent information on the clinical effectiveness safety of HFNC when compared with other NIVs in the treatment of acute hypoxemic respiratory failure in both COVID-19 and non-COVID-19 patients. We also aimed to capture and present the resource requirements and associated costs with the use of HFNC and other NIVs. Lastly, we also aimed to present the perspectives of patient groups on the use of non-invasive respiratory strategies (HFNC, other NIVs) on our ethical and social impact analysis.

CLINICAL PERFORMANCE

A. Review of evidence on the clinical effectiveness and safety of HFNC

Review of Reviews

A total of eight references were included in the qualitative data synthesis of our review – seven of which focused on clinical effectiveness, and one focused on clinical safety (aerosol generation).

Clinical Effectiveness

For clinical effectiveness, we found two completed systematic reviews (SRs) with meta-analysis (Sklar et al. 2018; Xu et al., 2018), one completed rapid review (RR) (Villanueva, Cruz & Palileo-Villanueva, 2020), and four ongoing and future studies/trials (Tverring, 2020; Gaulton, 2020; Zhang, 2020; Couper, 2020).

Both SRs (Sklar et al. 2018; Xu et al., 2018) covered non-COVID-19 patients with AHRF, while only the RR (Villanueva, Cruz & Palileo-Villanueva, 2020) covered COVID-19 patients with AHRF. One SR (Sklar et al. 2018) focused solely on immunocompromised patients while the the other SR (Xu et al., 2018) pooled studies regardless of the pre-existing conditions of the patients (e.g., patients with asthma, immunosuppressed). In terms of the intervention, HFNC was used. The review of Xu et al. (2018) covered two scenarios on the use of HFNC: first is when HFNC was used before intubation, and the second is when HFNC was used after extubation. All included reviews used other NIVs as comparator. In terms of the outcomes of interest of our rapid review, all reviews reported mortality and failure of respiratory support (escalation to invasive ventilation or rate of intubation). No review reported on length of hospital stay and length of ICU stay. The mean follow-up time is highly varied across reviews, which also depends on the outcome being measured. In terms of the study designs included, one review included randomized controlled trial (RCT) studies only (Xu et al., 2020), one review included observational studies only (Villanueva, Cruz & Palileo-Villanueva, 2020), and one review included both observational and RCT studies (Sklar et al., 2018).

There are four ongoing or future studies/trials on the use of HFNC for COVID-19 (Tverring, 2020; Gaulton, 2020; Zhang, 2020; Couper, 2020). The study/trial of Zhang (2020) is expected to be completed by February 2020, while the studies/trials of Tverring, (2020), Gaulton (2020), and Couper (2020) are expected to be completed by May 2021.

The reported results per outcome from the included SRs were as follows:

- **Mortality**

  Among COVID-19 patients with AHRF, one review (Villanueva, Cruz & Palileo-Villanueva, 2020) reported lower mortality (in general) in HFNC group when compared to NIV. The HFNC group had mortality rates of 0% to 81% as compared to 4.5% to 92% in the NIV

group. However, due to methodological limitations (i.e., variability in the study designs of the studies included, absence of controls, absence of control of confounders and potentially unequal baseline), the results were inconclusive.

For non-COVID-19 population:

- *Immunocompromised patients:* One review (Sklar et al., 2018) focused on immunocompromised non-COVID-19 patients. The reported pooled risk ratio on mortality rate using other NIVs as comparator was 0.60 (95% CI: 0.37-0.97, p=0.04). This translates to a *significant* (40%) reduction in the risk of mortality when using HFNC versus other NIVs. The reported statistical heterogeneity (I^2) of the subgroup analysis comparing HFNC and other NIVs was 52%, which was interpreted by the SR authors to be of *moderate* heterogeneity. GRADE assessment and publication bias were not reported in any of these results. We further note that there should be caution in interpreting these pooled estimates of Sklar et al. (2018). The results were pooled from studies of different study designs.

- **Failure of respiratory support (escalation to invasive ventilation) / Rate of intubation**

  Among COVID-19 patients with AHRF, the study of Villanueva, Cruz & Palileo-Villanueva (2020) reported higher failure of initial respiratory support in the HFNC group compared to NIV group. However, due to methodological limitations (i.e., variability in the study designs of the studies included, absence of controls, absence of control of confounders and potentially unequal baseline), the results were not conclusive.

  For non-COVID-19 population:

  - *Immunocompromised patients:* One review (Sklar et al., 2018) focused on immunocompromised non-COVID-19 patients. When HFNC was compared with other NIVs, the reported a pooled risk ratio of 0.67 (95% CI: 0.43-1.04, p=0.07) for rate of intubation and was considered as tending to benefit but not statistically significant. The reported statistical heterogeneity (I^2) of the pooling was 68%, which was interpreted by the SR authors to be of *high* heterogeneity. We further note that there should be caution in interpreting these pooled estimates of Sklar et al. (2018) as these were pooled from studies of different study designs and included a varied group of immunocompromised patients, hence the heterogeneity.

  - *Regardless of pre-existing patient conditions*: The study of Xu et al. (2018) reported a pooled odds ratio of 0.57 (95% CI: 0.36–0.92, p=0.02) for HFNC group versus NIV group and was noted to be statistically significant.

- **Length of hospital stay**

  No study compared HFNC with other NIVs in terms of length of ICU stay for both COVID-19 and non-COVID-19 population.

- **Length of ICU stay**

  No study compared HFNC with other NIVs in terms of length of ICU stay for both COVID-19 and non-COVID-19 population.

In terms of the reported risk of bias of the included reviews, overall, the RCTs analyzed for non-COVID-19 patients have a highly varied risk of bias using the Cochrane RoB tool while the included observational studies were generally of low risk of bias based on the Newcastle-Ottawa Scale for Observational Studies. On the other hand, the quality of studies for COVID-19 patients are generally unknown as no reported critical appraisal or risk of bias assessment was conducted in the included rapid review.

Our critical appraisal (using AMSTAR 2) of the included SRs (Sklar et al., 2018; Xu et al., 2018)) were assessed overall to be critically low. Commonly reported critical flaws were failure to explicitly report the following: protocol registration before the commencement of the review, justification for excluding individual studies, consideration of risk of bias when interpreting the results of the review, and assessment of presence and likely impact of publication bias. On the other hand, the included rapid review (Villanueva, Cruz & Palileo-Villanueva, 2020) adhered to four out of nine items in our devised adherence checklist (i.e., S*tudy Objectives, Search and Information Sources, Data Extraction,* and *Synthesis of Results*). The adherence checklist was based on the Cochrane Rapid Review Interim Guidance with some modifications to align it with the DOH-HTA Methods Guide. We note, however, that in the absence of a standard tool for the critical appraisal of rapid reviews, our evaluation does not rate the quality of said review, nor rapid reviews in general.

Overall, in terms of clinical effectiveness of HFNC among COVID-19 population, there is currently insufficient evidence to show the conclusive advantage of high flow nasal cannula (HFNC) for the treatment of Acute Hypoxemic Respiratory Failure (AHRF) among COVID-19 patients when compared to other NIVs. Ongoing and future trials are anticipated to provide stronger and more conclusive evidence on the relative treatment effect of using HFNC to treat COVID-19 patients with AHRF. These trials are expected to be completed by 2021. For the non-COVID-19 population, HFNC demonstrated a lower risk of mortality based on one SR involving immunocompromised patients when compared to other NIVs. In terms of rate of intubation, there were conflicting evidence on the ability of HFNC to lower the rate of intubation based on two systematic reviews. There were no included reviews that reported on outcomes length of hospital stay and length of ICU stay.

Clinical Safety (aerosol generation)

For COVID-19 population, we did not find any reviews demonstrating the safety of HFNC versus other NIVs based on aerosolization of respiratory droplets.

For the non-COVID-19 population, there is insufficient evidence to establish the clinical safety (in terms of aerosol generation) of HFNC when compared to other NIVs, although one study noted that increasing the pressure (CPAP) or flow rate (HFNC) would result to father distances traveled by the respiratory droplets.

Our critical appraisal (using AMSTAR 2) of the included SR (Agarwal et al., 2020) was assessed overall to be critically low. Commonly reported critical flaws were failure to explicitly report the following: protocol registration before the commencement of the review, justification for excluding individual studies, consideration of risk of bias when interpreting the results of the review, and assessment of presence and likely impact of publication bias.

Review of Local Studies

For the COVID-19 population, we did not find any local studies demonstrating the relative treatment effects of HFNC versus other NIVs based on the four clinical effectiveness outcomes assessed in this review. Studies from the Lung Center of the Philippines, Philippine General Hospital, St. Luke's Medical Center, and Philippine Heart Center are ongoing and are expected to be released in December 2020 or early 2021.

For the non-COVID-19 population, there is one RCT from the Philippine Heart Center (See et al., n.d.) demonstrating the relative treatment effects of HFNC versus NPPV (i.e., classified as NIV in this review). In all three outcomes assessed (i.e., ICU mortality, rate of intubation, length of hospital stay), HFNC did not demonstrate superior advantage over NPPV.

Based on our critical appraisal, the RCT was assessed to have high risk of bias.

Evidence gathered from expert opinion

Majority of the local experts consulted in this review are currently using HFNC specifically for COVID-19 patients with hypoxemic respiratory failure that do not need immediate intubation. . Most of the experts also observed that patients were more comfortable in using HFNC versus mechanical ventilation.

In terms of the risk of aerosolization, the panel had slightly varied opinions on the risk of transmission brought by HFNC and if it requires a negative pressure room. One expert stated that HFNC does not pose the risk of aerosolization at all. While, two experts stated that HFNC manifests this risk but is relatively lower as compared to other NIVs such as CPAP and BiPAP. Thus, other NIVs, as they emphasized, should not be used in COVID-19 patients due to higher risk of aerosolization of respiratory droplets. Three experts, on the other hand, noted that HFNC poses the risk of aerosolization, thus, they recommended it be done with a negative pressure HVAC (heating, ventilation, and air conditioning) system or a single room if the said technology is unavailable.

B. Review of clinical guidelines on the use of HFNC

Of the 15 countries/organizations reviewed for treatment guidelines on the use of HFNC, 11 (WHO, Philippines, Australia, Canada, China, Indonesia, Japan, Malaysia, UK, US, and Vietnam) have mentioned the use of HFNC in their guidelines. Recommendations were either weak, moderate, strong, or not indicated. Four guidelines (China, the Philippines, US, and Vietnam) have provided positive recommendations but with conditions for use; one guideline (UK) has provided a negative recommendation; and, six guidelines (WHO, Canada, Indonesia, Japan, Australia, and Malaysia) have provided several conditions where the use of HFNC is positively or negatively recommended.

C. Review of existing findings and recommendation from HTA agencies on the use of HFNC

None of the 13 HTA agencies reviewed have completed an assessment on the use of HFNC for COVID-19 patients with AHRF.

RESOURCE REQUIREMENTS AND ASSOCIATED COSTS

To obtain information on the human resource needs, training needs, consumables/accessories needed, special requirements (infrastructure, other equipment needed), projected initial and daily costs, and implementation concerns of HFNC and other NIVs, a standard questionnaire was sent to representatives of private and public hospitals that are using these treatment modalities. Additionally, an online panel consultation was conducted to obtain more information. The responses from the expert panel show that HFNC and other NIVs have similar requirements. Specifically, using HFNC and other NIVs will require the support of a pulmonologist, nurse and respiratory therapist and minimal training will be needed on the use of machines for both procedures. As for the consumables and equipment needed, HFNC and other NIVs will require the machine, various consumables and the oxygen supply. There are varying responses regarding the oxygen source needed for HFNC. Two respondents said that the oxygen source must be wall-mounted while one said that the HFNC machine can be connected to either a standard oxygen cylinder or an oxygen piping system. Another point of difference among respondents is that two hospitals require that a patient using HFNC be in a single room with a negative pressure system to mitigate the risk of aerosol generation and infection transmission. However, in one hospital, which does not have negative pressure rooms, such special room is not a requirement for HFNC.

Costs associated with HFNC and other NIVs vary with the severity of the patient's case and duration of treatment required. A patient using either form of oxygen therapy would have to pay for the initial set-up cost and daily costs for oxygen consumption, rental of machine use, and consumption of sterile water for injection. The initial set-up costs for HFNC and other NIVs across different hospitals range from Php 10,000.00 to Php 13,000.00and Php 6,754.00 to Php 14,549.25, respectively. The oxygen charged to the patient depends on the flow rate or FiO2 ordered by the pulmonologist which is on a case-by-case basis. In one public hospital, patients using HFNC at flow rates greater than 10L/min will still be charged the same rate for oxygen use at 9-10L/min. The daily rate for the use of the HFNC machine ranges from Php 1,100.00 to Php 2,030.00, while the daily rental of the machine for other NIVs ranges from Php 1,840.00 to Php 2,860.00. A patient using other NIVs would also be charged the cost for the bacterial filter which shall be replaced every 2-3 days. In terms of cost comparisons, while there is available data on the initial and daily costs associated with HFNC and other NIVs, there are still gaps on the average duration of treatment. Direct comparison of the costs associated with the two treatment modalities will not feasible.

There will only be minimal changes should health facilities adopt these health technologies. Applying HFNC and other NIVs for COVID-19 use will require additional precautions such as complete PPEs, separate wards and isolated rooms, and disinfection procedures to prevent transmission of infection due to the possible risk of aerosol generation.

ETHICAL AND SOCIAL ASSESSMENT

An online survey and a small group discussion were employed to elucidate patients' perspective on the different aspects of respiratory support strategies. Although the collected data revolved around the indirect experiences, situational questions, and perceptions, the results have shown that informants are more comfortable undergoing a procedure that is supported by their physician's recommendation. Informants displayed willingness to pay for a non-invasive respiratory support strategy such as HFNC even though its clinical benefits are yet be determined. It is important to note that they are willing to pay an additional cost or even exceed their financial capacity just to prevent or prolong the escalation to intubation. Lastly, informants also displayed the willingness to transfer to a hospital so that they may receive their preferred procedure.

The factors that the informants considered in their decision making in terms of respiratory support are the fear of escalation to intubation, and immobility as this would mean more expenses and may decrease the patient's quality of life. Communication plays a vital role in influencing the decision of the patient regarding respiratory support strategies. Whereas social support is expected from the patient's family to alleviate the fear and anxiety from the patient's experiences.

Results of the assessment showed that from a patient group perspective, the government should fund a non-invasive respiratory support strategy such as HFNC even though its clinical benefits are yet to be determined as long as it can prevent early intubation. Disinvestment should only be done when there is an established evidence that it is not effective. Even if the PhilHealth will remove non-invasive respiratory support strategies such as HFNC from its benefit package, the informants are willing to pay out of pocket. Overall, there was no identified legal issues, religious reasons, or cultural beliefs that inhibits a person from receiving non-invasive respiratory support strategy. A concern was raised regarding the applicability of non-invasive respiratory support strategies to tracheostomized patients. However, it should be noted that according to Dr. Minerva Calimag of HTAC Subcommittee on Medical and Surgical Procedures, HFNC can still be applied to the tracheostomy opening of these patients.

4. METHODOLOGY

4.1. Review of Clinical Evidence on HFNC

4.1.1. Review of evidence on the clinical effectiveness and safety of HFNC

In this rapid review, we identified three sources of evidence to establish the clinical effectiveness and safety of HFNC. First, we performed a review of reviews of existing published literature indexed in search databases. Second, we also performed a review of existing local studies from selected hospitals. Lastly, we sought clinical expert opinions of health professionals from various institutions.

4.1.1.1. Review of reviews

4.1.1.1.1 Literature Search Methods

As for the review of the effectiveness and safety of HFNC on treating AHRF, two reviewers performed a limited literature search of relevant studies using PubMed from inception to November 3, 2020. Search terms included the following and their variations: COVID-19 (using PubMed MeSH terms), Acute Hypoxemic Respiratory Failure (and its synonyms as identified by ICD10), high flow nasal cannula, high flow nasal oxygen. The LOVE database was also searched for systematic reviews on HFNC for AHRF. Ongoing and future studies/trials using HFNC for AHRF on COVID-19 patients were searched using ClinicalTrials.gov from inception to August 19, 2020.

There were no language restrictions in the targeted and systematic search. In the event that a non-English text was encountered and included in the review, Google Translate was intended to be used for the direct English translation of contents. In the systematic search for articles on the effectiveness and safety of HFNC on treating AHRF, there were no restrictions in the publication year as well.

4.1.1.1.2. Selection Criteria and Methods

Two reviewers independently screened the documents which were included in the review. The full text of potentially eligible studies with relevant abstracts and titles were retrieved and evaluated for eligibility using the set inclusion and exclusion criteria. Consensus was made in case of disagreement during the screening and/or full-text evaluation. While the policy and research questions were specific to COVID-19 population, we opted for an open population search and inclusion criteria in anticipation of limited published evidence on the use of HFNC for COVID-19 patients.

Table 1: Inclusion Criteria for systematic search	
Population	Any population with acute hypoxemic respiratory failure (including COVID-19 patients)
Intervention / Exposure	High-flow nasal cannula (HFNC) and its name synonyms: high-flow nasal oxygen (HFNO), High-flow nasal oxygen therapy (HFNOT), high flow oxygen therapy (HFOT)
Comparator	Other noninvasive ventilation [e.g., bilevel positive airway pressure [BiPAP], continuous positive airway pressure (CPAP)]

Outcomes	Effectiveness: Mortality, Failure of respiratory support* (escalation to invasive ventilation), Length of hospital stay, Length of ICU stay **Failure of respiratory support is defined as the failure of the current intervention (HFNC) or comparator (i.e., other NIVs) to provide respiratory support to the patient; hence, the treatment is switched to intubation.* Safety: Aerosol generation *** Aerosol generation is defined as the ability of the intervention (HFNC) or comparator (i.e., other NIVs) to release respiratory droplets or fine particles into the air.*
Study Designs	Systematic reviews (SRs) and rapid reviews (RRs)

Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 1 and if they were duplicate publications.

4.1.1.1.3. Data extraction and Management

The following information were extracted from the included studies/guidelines/references for the following characteristics:

Clinical effectiveness and safety	For completed studies: • Author and Year • Period of the systematic search • Conflict of interest declaration • Databases searched • Characteristics of included studies per SR/RR [in terms of Population (e.g., number of participants, patient characteristics), Intervention (e.g., settings description of HFNC), Comparator, and Outcome (reported results on mortality, rate of intubation, length of hospital stay, length of ICU stay, aerosol generation), Study designs included, corresponding number of included studies per study design) • Tool used in the risk of bias assessment per SR/RR and respective results For ongoing or future studies/trials: • Study ID & Title (Author, Year) • Status • Expected Study Completion Date • Study Design • Population (Location) • Intervention • Comparator • Outcomes to measure

4.1.1.1.4 Critical Appraisal

Information from studies obtained for the guidelines and effectiveness were extracted and summarized for key data domains mentioned above using a standard data extraction tool. Three reviewers performed critical appraisal of included studies. The *A Measurement Tool to Assess Systematic Reviews 2* (AMSTAR 2) (Shea et al., 2017) was used to critically appraise the included SRs. As for RRs, we did not find any critical appraisal tools that can be used to appraise such reviews. Hence, we devised a checklist using Cochrane's *Interim Guidance from the Cochrane Rapid Reviews Methods Group* (Garritty et al., 2020) with modifications to align with the Philippine HTA Methods Guide for developing Rapid Reviews. This checklist will determine if the included rapid reviews are consistent with the standards on performing a rapid review.

4.1.1.1.5. Data Synthesis

As this is a rapid review of reviews, we intended to perform qualitative synthesis and quantitative synthesis if appropriate. If the characteristics of the included studies are appropriate to be pooled, we intended to use DerSimonian and Laird random effects models to conduct the meta-analyses. All analyses were intended to be performed in RevMan 5.3. Study weights were intended to be generated using the inverse variance method. Risk ratios were intended to be used for dichotomous outcomes, while mean differences or standardized mean differences were intended to be used for continuous outcomes. In all pooled effects, 95% confidence intervals (CIs) were intended to be used.

The I^2 statistic was intended to be used to measure heterogeneity between studies. An I^2 value of 0-30%, 31-50%, 51-75%, and 76-100% indicate insignificant heterogeneity, moderate heterogeneity, substantial heterogeneity, and considerable heterogeneity, respectively. These ranges and interpretations were adapted from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019). Sources of heterogeneity were intended to be explored by doing various subgroup analysis based on the pre-identified variables (e.g. special populations with pre-existing conditions), when sufficient data were available.

4.1.1.2. Review of local studies

We consulted selected local public and private hospitals to determine existing local studies on HFNC. The list of the hospitals was identified by the members of the HTA Council. Studies provided by the experts were used to supplement our rapid review.

Two reviewers independently screened and extracted the documents which were included in the review. Same eligibility criteria were applied (see Table 1), except on the study design which we opened to all types of study designs. Consensus was made in case of disagreement during the screening and/or full-text evaluation.

Two reviewers independently performed critical appraisal of included studies. The *Cochrane RoB2 Tool* (Stern et al. 2019) was used to critically appraise randomized trials. For cohort and observational studies, the Newcastle-Ottawa Assessment Scale (Wells et al., n.d.) was intended to be used.

4.1.1.3. Evidence gathered through expert opinion

We consulted various clinical experts from different medical societies and hospitals regarding their clinical experience on the use of HFNC for COVID-19. The list of professional societies included relevant specialties involved in the care of COVID-19 patients (I.e., critical care, internal

medicine, pulmonology, infectious disease, critical care nursing and respiratory therapy). Experts were then nominated by their respective medical societies.

Key experts from major COVID-19 referral hospitals were also identified to obtain their experience on the use of different oxygenation strategies.

Standard questionnaires were sent via email (see Appendix 1). Experts were also invited to participate in an online panel consultation to further clarify their responses. We note that in the conduct of expert panel consultation, answering all questions were not mandatory for the participants. Further, we did not intend to have them collectively agree on each discussion point raised. All experts were asked to sign the Declaration of Conflict of Interest Form (COI Form) and Non-Disclosure Agreement (NDA Form).

Local allied and medical professional societies consulted	• Critical Care Nurses Association of the Philippines, Inc. • Philippine College of Chest Physicians • Philippine Neuro-Critical Care Society • Philippine Society of Critical Care Medicine • Respiratory Therapists Society • Society of Pediatric Critical Care Medicine
Local hospitals consulted	• Lung Center of the Philippines • Philippine General Hospital • Philippine Heart Center • St. Luke's Medical Center • The Medical City

Our questions were designed to obtain information on HFNC's place in the current COVID-19 treatment pathway, first-hand clinical experience regarding its use, adverse events associated with its use, and awareness on locally conducted studies or other sources of data. Initially, we were able to collect data on HFNC as compared with COT. However, given the evolving evidence on COVID-19, it was noted that both were not the appropriate comparators for HFNC. HFNC serves as a rescue therapy for COVID-19 patients with AHRF who did not improve despite administration of COT.

Key points from the responses were narratively reported.

4.1.2. Review of clinical guidelines and existing findings and recommendation from HTA agencies on the use of HFNC

4.1.2.1. Literature Search Methods

Two reviewers conducted the search on November 5, 2020 for the treatment guidelines of selected international or country-specific guidelines, and positions or assessment recommendations from selected HTA agencies regarding the use of HFNC on COVID-19 patients with acute hypoxemic respiratory failure (AHRF). Through a targeted search, treatment guidelines and HTA agency reports of the following countries were reviewed regarding the use of HFNC on COVID-19 patients:

Treatment Guidelines	15 testing guidelines from WHO, European Center for Disease Control (ECDC), Australia, Canada, China, Indonesia, Japan, Malaysia, Philippines Singapore, South Korea, Thailand, United Kingdom (UK), United States of America (USA), and Vietnam
Review of evidence synthesis from HTA agencies	13 HTA agencies from EUnetHTA, Australia, Canada, China, Indonesia, Malaysia, Philippines Singapore, South Korea, Thailand, UK, US, and Vietnam

4.1.2.2. Data extraction and Management

Information from studies obtained from the guidelines and HTA agencies were extracted and summarized for key data domains mentioned using a standard data extraction tool. The following information were extracted:

Treatment Guidelines	• Country of origin • Guideline details on the use of HFNC as part of treatment for AHRF in COVID-19 patients
Review of evidence synthesis from HTA agencies	• Country of origin • Originating HTA agency of the guidelines • Position/Recommendation on the use of HFNC as part of treatment for AHRF in COVID-19 patients

4.2. Resource requirements and associated costs

To obtain resource requirements and associated costs on the use of HFNC, we also consulted representatives from private and public hospitals, and DOH offices. We sent out a standard questionnaire through electronic mail. To gather more evidence, we also invited them for an online panel consultation. We note that in the conduct of expert panel consultation, answering all questions were not mandatory for the participants. Further, we did not intend to have them collectively agree on each discussion point raised. All representatives external of DOH were asked to sign the Declaration of Conflict of Interest Form (COI Form) and Non-Disclosure Agreement (NDA Form).

Local hospitals consulted	• East Avenue Medical Center • Lung Center of the Philippines • Philippine General Hospital • Philippine Heart Center • St. Luke's Medical Center – Bonifacio Global City • The Medical City
DOH offices consulted	• Health Facilities and Services Regulatory Bureau (HFSRB) • Health Facilities Development Bureau (HFDB) • Health Facilities Enhancement Program (HFEP)

Our questions were designed to obtain information on human resource needs, training needs, consumables/accessories needed, special requirements (infrastructure, other equipment needed),

projected initial and daily costs, and implementation concerns. Initially, we were able to collect data on HFNC as compared with COT and invasive/mechanical ventilation. However, given the evolving evidence on COVID-19, it was noted that both were not the appropriate comparators for HFNC. HFNC serves as rescue therapy for COVID-19 patients with AHRF who did not improve despite administration of COT. In addition, HFNC serves as a "bridging" intervention (or intermediate step) before invasive/mechanical ventilation.

Key points from the responses were narratively reported. The standard questionnaire that was used can be found in Appendix 2.

4.3. Ethical and social impact assessment

To assess the ethical and social impact, we consulted patient groups on their perspectives regarding the use of various respiratory support strategies for COVID-19. Relevant patient groups from the Health Technology Assessment Unit stakeholder consultation database were identified. Relevant patient groups are those groups advocating for awareness on respiratory illnesses, and umbrella patient organization/s. To expand the pool of patient organizations to be consulted, referrals from the pre-identified organizations from the consultation database were also requested. Identified patient groups then nominated representatives who received the questionnaires beforehand and were asked to accomplish a Declaration of Conflict of Interest Form (COI Form), and Informed Consent Form (ICF).

Two sets of questionnaires were designed for the patient group consultation. These were reviewed and approved by the ethics practitioner, anthropologist, and citizens' representative of the HTA Council Core Committee. The first set was administered through Google Forms which primarily asks for personal experiences on difficulty in breathing and the use of HFNC, and preference and willingness to pay on various respiratory support strategies. The second set was used in an online small group discussion (SGD). The questions in the SGD were designed to capture information related to preferences, perceived risks and benefits, and concerns on funding of various respiratory support strategies. Furthermore, both sets of questionnaires were written in English and Filipino language and came with briefers which discussed the context of this review and basic information about different respiratory support strategies. This is to level off the knowledge of the informants and facilitate their decision making. The content of the informed consent forms was also explained prior to the start of the SGD and the informants' verbal consent were elicited. Key points from the responses were narratively reported. Initially, we were able to collect data on HFNC as compared with COT. However, given the evolving evidence on COVID-19, it was noted that COT was not the appropriate comparator for HFNC considering that HFNC serves as rescue therapy for COVID-19 patients with AHRF who did not improve despite administration of COT.

The questionnaires that were used can be found in Appendix 3a and 3b.

5. SUMMARY OF EVIDENCE

5.1. Review of Clinical Evidence on HFNC

5.1.1 Review of evidence on the clinical effectiveness and safety of HFNC

5.1.1.1 Review of reviews

5.1.1.1.1 Quantity of included studies

Figure 2 illustrates the PRISMA flowchart for the study selection. Records identified through database searching (PubMed, LOVE database, Clinicaltrials.gov) yielded a total of 711 records. An additional record (n=1) was identified through search on PSMID website. After removing the duplicates, 704 title and abstract entries were screened. Of these, 675 articles were excluded leaving 28 articles for full-text review. Among the 28 records, 21 records were excluded due to the following reasons: 1 study did not have full-text available; 2 studies did not include the population of interest; 1 study did not include intervention of interest; 2 studies did not include comparator of interest; 1 study did not include the outcome of interest; 4 studies did not include the study design of interest; while 10 records were not the most recent and more comprehensive systematic reviews. The characteristics of excluded studies can be found in Appendix 4. An additional article (n=1) was retrieved during the full-text screening. In total, 8 records were included in qualitative data synthesis which consist of 3 completed SRs, 1 completed RR, and 4 ongoing and future studies/trials.

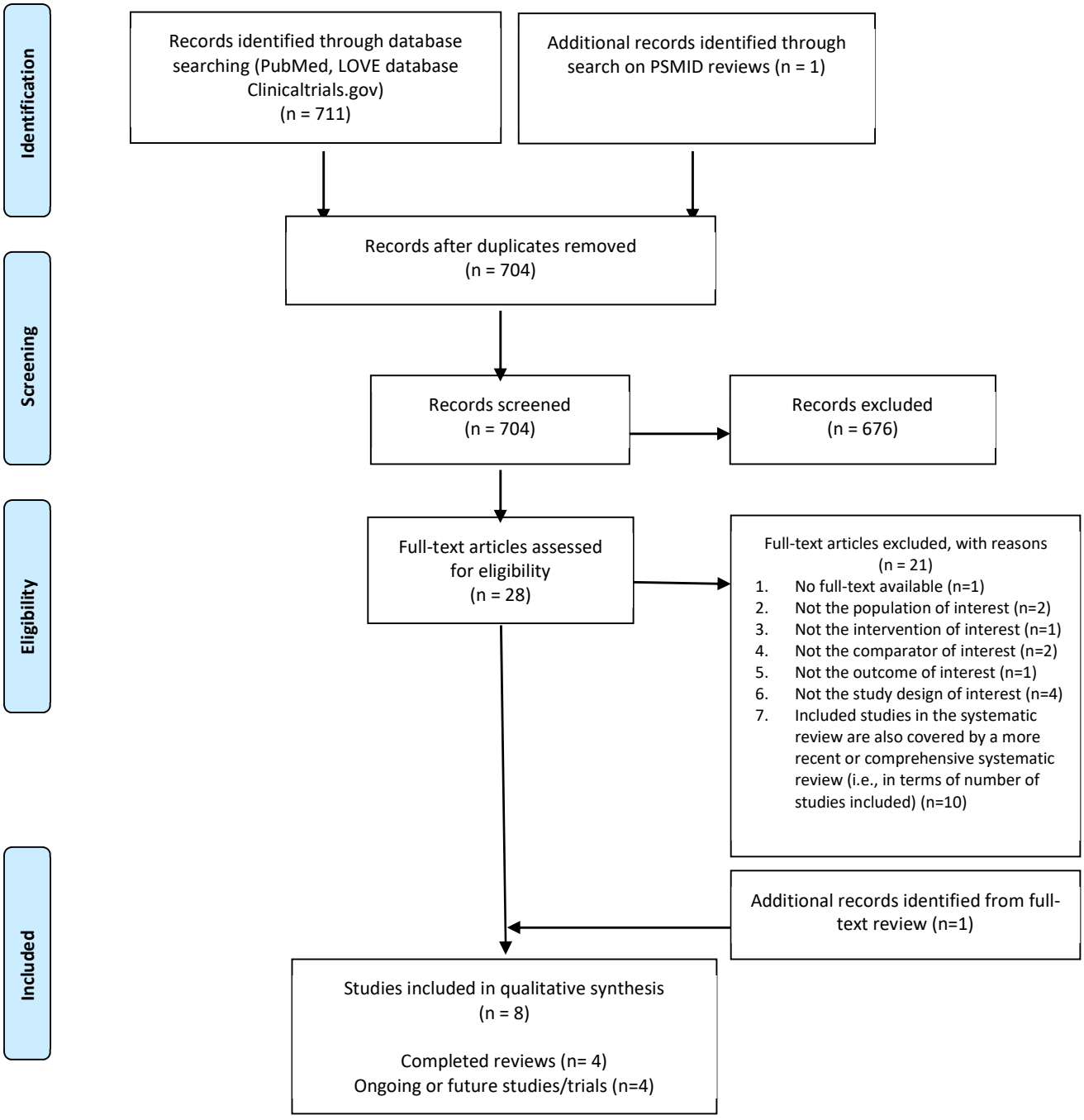

Figure 1. PRISMA flow diagram of systematic search for clinical effectiveness and safety reviews or studies

5.1.1.1.2 Characteristics of included reviews or studies

5.1.1.1.2.1 Completed reviews

Of the four included reviews, two are SRs with meta-analysis (Sklar et al. 2018; Xu et al., 2018), one SR without meta-analysis (Agarwal et al., 2020) and one RR (Villanueva, Cruz & Palileo-Villanueva, 2020). Table 2 characterizes the included completed reviews.

Clinical effectiveness

For the clinical effectiveness, there were three included reviews. Two were SRs with meta-analysis (Sklar et al. 2018; Xu et al., 2018), and one RR (Villanueva, Cruz & Palileo-Villanueva, 2020).

- In terms of population, all two SRs covered non-COVID-19 patients with AHRF, while only the RR covered COVID-19 patients with AHRF. One SR (Sklar et al. 2018) focused solely on immunocompromised patients while Xu et al. (2018) pooled studies regardless of the pre-existing conditions of the patients (e.g., patients with asthma, immunosuppressed). In terms of the intervention, HFNC was used. The review of Xu et al. (2018) covered two scenarios on the use of HFNC: first is when HFNC was used before intubation, and the second is when HFNC was used after extubation. In terms of the comparator, all three reviews included other NIVs as comparator. Other comparator which is not part of our research question but was reported by the reviews is conventional oxygen therapy (COT). In terms of the outcomes of interest of our rapid review, all reviews reported mortality and failure of respiratory support (escalation to invasive ventilation or rate of intubation). No review reported on length of hospital stay and length of ICU stay. Other outcomes which are not part of our research question but were reported by the reviews are as follows: patient comfort (Xu et al., 2018), respiratory rate (Xu et al., 2018), and P/F ratio (Xu et al., 2018). The mean follow-up time is highly varied across reviews, which also depends on the outcome being measured. In terms of the study designs included, one review included randomized controlled trial (RCT) studies only (Xu et al., 2020), one review included observational studies only (Villanueva, Cruz & Palileo-Villanueva, 2020), and one review included both observational and RCT studies (Sklar et al., 2018).

Clinical safety in terms of aerosolization associated with HFNC

For clinical safety of HFNC in terms of aerosol generation associated with HFNC, we only found one review (Agarwal et al. 2020). We describe it as follows:

- In terms of population, the SR included healthy adults, simulated models, and critically ill patients. None of the included studies in the SR focused on COVID-19 population. In terms of the comparator, the included studies were comparing HFNC with other NIVs (i.e., CPAP). It also included a comparator (i.e., HFNC vs no HFNC, HFNC vs COT) which was not part of our research question. The outcomes reported were droplet dispersion distance, percentage leakage of aerosolized droplets, and microbial colony counts in air and surface samples. In terms of the study design included, majority were simulation studies and one crossover study.

Table 2. Characteristics of included completed reviews

Author of the RR/SR (Year)	Period of systematic search	COI declared? (Y/N)	Databases searched	Characteristics of included studies in the SR						Corresponding number of included studies per study design
				Population	Intervention	Comparator	Outcome	Mean Follow-up Time	Study designs included	
Included reviews on clinical effectiveness										
Sklar et al. (2018) (SR with Meta-analysis)	Inception through May 15, 2018	Y	MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Clinical Trials, CINAHL, Clinicaltrials.gov, PubMed and non-PubMed records	n=545 The study included cases of immunocompromised population with acute hypoxic respiratory failure. Different causes were attributed to immunosuppression (I.e., oncologic diagnosis with a predominance of hematologic malignancy, solid organ transplant, infectious pneumonia, opportunistic infections and fungal infections).	HFNC Duration of HFNC therapy: Varied widely, ranging from 2 h to 80 h FIO2: ranged from 0.60 to 1.00 with flows of 21–60 L/min Location: HFNC was initiated in the emergency department, acute care ward, or ICU, with the latter being the most common site of initiation (10 of 13 studies).	Oxygen therapy control (other NIV)	Rates of intubation: Varied across the studies given the variable time points of assessment.	28 days on mortality	Match cohort	1
								Not reported	Retrospective, cohort study	1
								90 days on mortality	Prospective, observational study	1
								Varies (ranges from 28 days to 90 days on mortality)	RCT	1 (post-hoc analysis of previous RCTs)

Author of the RR/SR (Year)	Period of systematic search	COI declared? (Y/N)	Databases searched	Characteristics of included studies in the SR						
				Population	Intervention	Comparator	Outcome	Mean Follow-up Time	Study designs included	Corresponding number of included studies per study design
Xu et al (2018)	Inception through September 1, 2018	Y	Pubmed, EMBASE, Scopus, and Web of Science	n =420	HFNC was defined as respiratory support that delivered a high flow (> 15 L/min) of heated and humidified oxygen (37 °C) administered through nasal cannula 2 trials (n= 420) compared HFNC to NIV as an initial support strategy.	NIV included bilevel positive airway pressure and continuous positive airway pressure (CPAP).	Primary outcomes: Treatment failure and intubation (alternatively, reintubation rate in trials comparing alternative treatments after extubation) reflecting the efficacy of HFNC therapy (i.e., HFNC vs. COT, HFNC vs. NIV). Secondary outcomes included ICU and hospital mortality, ICU and hospital length of stay (LOS), patient comfort, respiratory rate (RR), and P/F ratio outcomes.	NR	Prospective RCT	2
Villanueva, Cruz & Palileo-Villanueva (2020)	No period reported	Y	PubMed, CENTRAL, ClinicalTrials.gov, ISRCTN Registry, medRxiv, UpToDate (date of last search: April 21, 2020) Twitter feed of PSMID and PCP (date of last	n=526 COVID-19 patients from China, with some studies including severe and critically ill patients, as well as those who experienced severe acute respiratory failure (summary measures of patient characteristics across studies not reported)	HFNC (details not reported)	NIV (details not reported)	Reported outcomes (1) Failure of Respiratory Support (2) Mortality (3) Safety	Five out of 6 case series reported mortality follow-up (28 days)	Case series	6
								Not reported	Before and after comparison	1

Author of the RR/SR (Year)	Period of systematic search	COI declared? (Y/N)	Databases searched	Characteristics of included studies in the SR						
				Population	Intervention	Comparator	Outcome	Mean Follow-up Time	Study designs included	Corresponding number of included studies per study design
			search: April 24, 2020)							
Included reviews on clinical safety in terms of aerosolization associated with HFNC										
Agarwal et al. (2020)	1 January 2007 to 14 May 2020.	Y	Ovid MEDLINE and Embase	n=28 (count excluding studies which use of simulators) Population included healthy adults, critically ill patients with gram negative stain, in silico simulator*, patient simulator** * in silico simulator - experiment performed through a computer **patient simulator - use of computer-driven mannequin to mimic real patients	HFNC (at varying flow rates)	NIV	Study outcomes included the (1) number, diameter, evaporation rates, and velocity of exhaled aerosols; (2) regions of high aerosol density; (3) droplet dispersion distance; and (4) microbial colony counts in air and surface samples	N/A	Simulation studies	3
									Crossover study	1

Note: **Y:** Yes| **N:** No | **NR:** Not reported | **N/A:** Not applicable

5.1.1.1.2.2. Ongoing and future studies/trials

We found four ongoing or future studies/trials on the use of HFNC for COVID-19 (Tverring, 2020; Gaulton, 2020; Zhang, 2020; Couper, 2020). The study of Zhang (2020) is expected to be completed by February 2020, while the trials of Tverring, (2020), Gaulton (2020), and Couper (2020) are expected to be completed by May 2021.

All identified ongoing or future studies/trials involved COVID-19 patients as study population – two of which included patients who also suffered from acute hypoxic respiratory failure (Tverring, 2020; Gaulton, 2020). In terms of the location of where the study is/will be conducted, one study is from Europe (Tyerring, 2020), two in Asia (Zhang, 2020; Couper, 2020), and one (Gaulton, 2020) in North America. HFNC was the intervention of focus for these studies. One study (Couper, 2020) utilized COT, HFNC, and NIV in its intervention (i.e., mild cases with COT, moderate/severe cases with NIPPV or HFNC). Comparators tagged in these studies were CPAP helmet (Tverring, 2020; Gaulton, 2020), and NIV (Zhang, 2020). Meanwhile, one study (Couper, 2020) did not specify its comparator. Outcomes measured among these studies were include ventilator-free days (Tverring, 2020; Gaulton, 2020), short-term mortality (Couper, 2020) and incidence of respiratory failure (Zhang, 2020; Couper 2020).

Table 3 characterizes the included ongoing and future studies/trials on the use of HFNC for COVID-19.

Table 3. Characteristics of included ongoing or future trials on the use of HFNC for COVID-19

Study ID & Title (Author, Year)	Status	Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
NCT04395807 Helmet CPAP Versus HFNC in COVID-19 (COVID HELMET) (Tverring, 2020)	Recruiting	May 2021	RCT	Patients admitted to Helsingborg Hospital, Sweden, suffering from COVID-19 and an acute hypoxic respiratory failure (Sweden)	HFNC	Continuous Positive Airway Pressure (CPAP) Helmet	Primary outcome: (1) Ventilator-Free Days (VFD) Secondary outcome: (1) SpO_2/FiO_2-ratio (2) Patient comfort (3) Frequency of endotracheal intubation (4) Frequency of CO_2 rebreathing (5) Days alive within
NCT04381923 COVIDNOCHE Trial (HFNO Versus CPAP Helmet) in COVID-19 Pneumonia (COVIDNOCHE) (Gaulton, 2020)	Not yet recruiting	May 15, 2021	RCT	Patients with acute hypoxemic respiratory failure from COVID-19 pneumonia (USA)	HFNC	CPAP Helmet	Primary outcome: (1) Ventilator-Free Days (VFD) Secondary outcome: (1) ICU and Hospital Length of Stay (2) Intubation (3) Renal replacement therapy (4) Mortality

Study ID & Title (Author, Year)	Status	Expected Study Completion Date	Study Design	Population (Location)	Intervention	Comparator	Outcomes to measure
NCT04312100 Sequential Oxygen Therapy Strategy for Patients With COVID-19 (SOTSPC) (Zhang, 2020)	Recruiting	February 2021	Prospective cohort	Only patients diagnosed with COVID-19 will be enrolled, diagnosis will depend on RT-PRC provided by China CDC (China)	HFNC	NIPPV, COT	Primary outcome: (1) Incidence of respiratory failure Secondary outcome: (1) 28 day mortality rate
ISRCTN16912075 RECOVERY Respiratory Support: Respiratory Strategies in patients with coronavirus COVID-19 – CPAP, high-flow nasal oxygen, and standard care (Couper, 2020)	Recruiting	May 5, 2021	Adaptive pragmatic open-label multicenter RCT	COVID-19 diagnosed by RTPCR Ages 18-75 years (Zhengzhou, Henan, China)	Mild cases with conventional oxygen therapy Moderate/Severe cases with nasal high flow oxygen inhalation Moderate/Severe cases with noninvasive positive pressure ventilation	Not specified	Incidence of respiratory failure 28-day mortality rate

5.1.1.1.3. Reported findings of the included reviews

5.1.1.1.3.1. Reported RoB assessment of the included studies in the SRs or RRs

The reported risk of bias (RoB) assessment of the included RCT studies in the SRs or RRs is summarized in Table 4, while the reported RoB assessment for the included observational studies is summarized in Table 5.

Clinical effectiveness

There were three included reviews on clinical effectiveness, two of which used the Cochrane Collaboration Risk of Bias (RoB) Tool for the assessing the risk of bias of the included studies (Xu et al., 2018; Sklar et al., 2018). Sklar et al. (2018) also used the Newcastle-Ottawa Scale for Observational Studies for assessing the risk of bias of observational study designs. Villanueva, Cruz & Palileo-Villanueva (2020) did not mention performing risk of bias assessment.

In terms of the general RoB assessment findings per domain of the included RCTs across the SRs (Sklar et al., 2018; Xu et al., 2018), the domains *random sequence generation, allocation concealment, incomplete outcome data, selective reporting,* and *other bias* were generally noted to be of low risk of bias. The domain *blinding of outcome assessment* was generally noted to be of low risk of bias for the included studies in Xu et al., 2018, while it was generally noted to be high risk of bias for the included studies in Sklar et al. (2018). It was notable that across the included studies of the reviews, there is a high risk of bias in the domain *blinding of participants and personnel*. It is important to note, however, that in the review of Sklar et al. (2018), the domains *blinding of participants and personnel* and *blinding of outcome assessment* were reported as *blinding* only. For the purposes of this review, we interpreted this as the RoB result for both domains.

In terms of the general RoB assessment findings per domain of the included observational studies of Sklar et al. (2018), the studies were generally compliant on the domains *Selection* and *Outcome*. For the *Comparability* domain, seven out of 9 included studies were compliant.

In terms of assessment of the overall RoB of each included study per review, the included RCT studies in the review of Sklar et al. (2018) were generally assessed to be of low risk of bias. For the included observational studies in the said review, it was reported that they were of moderate to high quality, ranging from 6 to 9 points. Xu et al. (2020) did not report their overall RoB assessment.

Overall, the RCTs analyzed in the included systematic reviews for non-COVID-19 patients have varying risks of bias using the Cochrane RoB tool while the included observational studies were generally of low risk of bias based on the Newcastle-Ottawa Scale for Observational Studies. On the other hand, the quality of studies for COVID-19 patients are generally unknown as no critical appraisal or risk of bias assessment was conducted in the included rapid review.

Clinical safety in terms of risk of aerosolization

Agarwal et al. (2020) did not report risk of bias assessment of the included studies in their review.

Table 4. Reported Risk of Bias (RoB) assessment of the included RCT studies in the SRs or RRs

Author of the SR (Year)	Study designs included	Corresponding number of included studies per study design	Tool used for assessing RoB per study design	Author of the included study (Year)	RoB assessment domains[A]							
					Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall RoB assessment
Reported RoB of included reviews on clinical effectiveness												
Sklar et al. (2018)	RCT	1	Cochrane Collaboration Risk of Bias Tool	Frat (2015)	High	Low	High (reported as "blinding" in the study)		Low	Low	NR	Unclear
Xu et al (2018)	RCT	2	Cochrane Collaboration Risk of Bias Tool	Doshi et al (2018)	Low	Low	High	Unclear	Low	Low	Low	NR
				Frat et al (2015)	Low	Low	High	Unclear	Low	High	Low	NR
Villanueva, Cruz & Palileo-Villanueva (2020)	No RoB											
Reported RoB of included reviews on clinical safety in terms of aerosol generation												
Agarwal et al. (2020)	No RoB											

Notes: **RoB:** Risk of Bias | **NR:** Not reported | **[A]:** In the review of Sklar et al. (2018), the domains *Blinding of participants and personnel* and *Blinding of outcome assessment* were reported as *Blinding* only. For the purposes of this review, we interpreted this as the RoB result for both domains.

Table 5. Reported Risk of Bias (RoB) assessment of the included observational studies in the SRs or RRs

Author of the SR (Year)	Study designs included	Corresponding number of included studies per study design	Tool used for assessing RoB per study design	Author of the included study (Year)	RoB assessment domains								Score
					Selection				Comparability	Outcome			
					Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts based on design and analysis	Assessment of outcome	Timing of follow-up	Adequate follow-up	
Reported RoB of included reviews on clinical effectiveness													
Sklar et al. (2018)	Prospective cohort	1	Newcastle-Ottawa Scale for Observational Studies	Coudroy et al. (2016)	/	/	/	/	//	/	/	/	9
	Matched cohort	1		Azoulay et al. (2017)	/	/	/	/	*	/	/	/	7
	Retrospective cohort	1		Tu et al. (2017)	/	/	/	/	//	/	/	/	9

Note:
*Author of the SR's note: propensity score analysis conducted but raw data used for this analysis as did not have access to propensity score data breakdown

5.1.1.1.3.2. Quantitative results of the reviews

The quantitative results of the reviews summarized in Table 6.

Clinical effectiveness

I. <u>Outcome #1: Mortality</u>

The included reviews reported on mortality outcome in terms of hospital mortality (Xu et at., 2018), or mortality in general (Sklar et al., 2018; Villanueva, Cruz & Palileo-Villanueva, 2020).

A. For the COVID-19 population:

The study of Villanueva, Cruz & Palileo-Villanueva (2020) reported lower mortality (in general) in HFNC group when compared to NIV. However, due to methodological limitations (i.e., variability in the study designs of the studies included, absence of controls, absence of control of confounders and potentially unequal baseline), the results were only narratively described. The HFNC group had mortality rates of 0% to 81% as compared to 4.5% to 92% in the NIV group.

B. For the non-COVID-19 population

i. Immunocompromised population subset (Sklar et al., 2018)

For the analysis on mortality using other NIVs as comparator, the reported pooled risk ratio was 0.60 (95% CI: 0.37-0.97, p=0.04). This translates into a significant (40%) reduction in the risk of mortality when using HFNC versus other NIVs. However, there should be caution in interpreting the pooled estimate as this was pooled from studies of different study designs. No justification on this pooling method was given by the review authors. The pooled result of the subgroup analysis came from included RCTs and cohort studies (4 studies, n=545). The reported statistical heterogeneity (I^2) of the pooling was 52%, which was interpreted by the SR authors to be of *moderate* heterogeneity.

GRADE assessment and publication bias were not reported in any of these results.

II. <u>Outcome #2: Failure of Respiratory Support / Rate of Intubation</u>

All included reviews reported on failure of respiratory support/rate of intubation outcome.

A. For the COVID-19 population (Villanueva, Cruz & Palileo-Villanueva, 2020)

The study of Villanueva, Cruz & Palileo-Villanueva (2020) reported rate of intubation of HFNC when compared to NIV. The failure of initial respiratory support was higher among patients on HFNC compared with NIV in 2 studies (case series and retrospective study). However, due to methodological limitations (i.e., variability in the study designs of the studies included, absence of controls, absence of control of confounders and potentially unequal baseline), the results were not conclusive.

B. For the non-COVID-19 population:

i. Immunocompromised population subset (Sklar et al., 2018)

For the subgroup analysis of rate of intubation using other NIVs as comparator, the reported pooled risk ratio was 0.67 (95% CI: 0.43-1.04, p=0.07) from 4 studies. It was noted, however, that the pooled result was not significant. The pooled result of the subgroup analysis came from included RCTs and cohort studies (4 studies, n=545). However, there should be caution in interpreting the pooled estimate as this was pooled from studies of different study designs. No justification on this pooling method was given by the review authors. The reported statistical heterogeneity (I^2) of the pooling was 68%, which was interpreted by the SR authors to be of high heterogeneity.

GRADE assessment and publication bias were not reported in all the above-mentioned results.

ii. Regardless of pre-existing patient characteristics (e.g., with asthma, immunocompromised) subset (Xu et al., 2018)

Only the study of Xu et al. (2018) reported on the rate of intubation of HFNC when compared with other NIVs as initial support strategy. It reported a pooled odds ratio of 0.57 (95% CI: 0.36–0.92, p=0.02) for the rate of intubation when HFNC was compared with NIV and was noted to be statistically significant. The pooled result of the subgroup analysis came from included RCTs (2 studies, n=420). This translates into a significant (43%) reduction in the need for intubation among those in the HFNC group compared to other NIVs (as initial support strategy) group. The reported statistical heterogeneity (I^2) of the pooling was 0%, to which no interpretation was given by the SR authors. Furthermore, using GRADE assessment tool, the SR authors graded the certainty of evidence as *low,* with a potential publication bias based on the funnel plot. The SR authors noted, however, that they did not construct funnel plots as fewer than 10 trials were identified for the comparison between HFNC and NIV.

III. <u>Outcome #3: Length of Hospital Stay</u>

No study was found comparing HFNC with other NIVs in terms of length of hospital stay for both COVID-19 and non-COVID-19 population.

IV. <u>Outcome #4: Length of ICU Stay</u>

No study was found comparing HFNC with other NIVs in terms of length of hospital stay for both COVID-19 and non-COVID-19 population.

Clinical safety in terms of aerosolization associated with HFNC

Due to the different study designs of the studies included in their SR, Agarwal et al. (2020b) narratively reported their findings and did not perform meta-analysis. The population of the included studies focused on the non-COVID-19 population. Specifically, the population of the included studies were a mix of healthy adults, critically ill patients with pneumonia caused by gram-negative bacteria, *in silico* simulator (experiment performed through a computer), or patient simulator (use of computer-driven mannequin to mimic real patient). We are reporting the results of the included studies in the systematic review of Agarwal et al. (2020b).

I. Measure #1: Distance traveled by respiratory droplets

One study used a human patient simulator to compare the distance of respiratory droplets when using HFNC or CPAP (i.e., CPAP is classified as "Other NIV" in this review). The study simulated different severities of lung injury in a negative pressure room, and also tested the effects of increasing the flow rates (for HFNC) or pressure (for CPAP) on the distance traveled by the respiratory droplets. It was observed that there is an inverse trend on the severity of lung injury and distance traveled by respiratory droplets; the more severe the lung injury, the lesser the distance traveled by the respiratory droplets. Conversely, it was observed that the higher the flow rates of HFNC, the farther the distance traveled by the droplets (6.5 ± 1.5 cm at 10 L/min to 17.2 ± 3.3 cm at 60 L/min). This trend was observed to be significant ($p < 0.001$). Similar result was observed for CPAP: increasing the positive pressure resulted to farther distance traveled by droplets (186±34 to 264±27 mm and from 207±11 to 332±34 mm when CPAP was increased from 5 to 20 cm H_2O). We noted, however, that the study did not directly compare HFNC and CPAP.

II. Measure #2: Percentage leakage of aerosolized particles

No study reported aerosolization comparing HFNC with other NIVs in terms of percentage leakage of aerosolized particles.

III. Measure #3: Degree of environmental bacterial contamination

No study reported aerosolization comparing HFNC with other NIVs in terms of degree of environmental bacterial contamination.

Table 6. Quantitative results of the included SRs or RRs

Author of the SR (Year)	Intervention	Comparator	Outcome	Study design	Number of studies considered for the outcome (with n expressed as total number of participants)	Statistical model (fixed/random effects)	Heterogeneity (I^2 %)	Pooled treatment effect OR any measure reported (expressed as RR, OR, % etc with confidence interval, whenever applicable), p-value, S/NS (if applicable)	GRADE Assessment (if reported)	Publication bias (if reported - method, result)
Quantitative results of included reviews on clinical effectiveness										
Sklar et al. (2018)	HFNC	NIV	Mortality	Mixed (RCT and cohort studies)	4 studies (n=545)	Random effects	I^2=52%	Pooled RR: 0.60 [95% CI: 0.37-0.97], p=0.04, S	NR	NR
			Rates of intubation	Mixed (RCT and cohort studies)	4 studies (n=545)	Random effects	I^2=68%	Pooled RR: 0.67 [95% CI: 0.43-1.04], p=0.07, NS	NR	NR
Xu et al. (2018)	HFNC	Subgroup: NIV (initial support strategy)	intubation rate	RCT	2 studies (n=420)	Fixed effects	I^2=0%	OR 0.57; 95%CI 0.36–0.92; p = 0.02, S	Low	Funnel plot showed potential publication bias
			ICU Mortality	RCT	1 study (n=216)	Random effects	NR	NR	NR	NR
			Hospital mortality	RCT	NR	Random effects	NR	NR	NR	NR
			ICU length of stay	RCT	NR	Random effects	NR	NR	NR	NR
			Hospital length of stay	RCT	NR	Random effects	NR	NR	NR	NR
Villanueva, Cruz & Palileo-Villanueva (2020)	HFNC	NIV	Mortality	Case series	5 studies	Not applicable	Not applicable	Review reported individual mortality rates per included study HFNC Liao: 0/31 (0%) Luo: 74/106 (70%) Wang Y: 28/35 (80%) Yang: 16/33 (48%) Zhou: 33/41 (81%) NIV Liao: 1/22 (4.5%) Luo: 48/56 (86%) Wang Y: 27/34 (79%) Yang: 23/29 (79%) Zhou: 24/26 (92%)	NR	NR

Author of the SR (Year)	Intervention	Comparator	Outcome	Study design	Number of studies considered for the outcome (with n expressed as total number of participants)	Statistical model (fixed/random effects)	Heterogeneity (I^2 %)	Pooled treatment effect OR any measure reported (expressed as RR, OR, % etc with confidence interval, whenever applicable), p-value, S/NS (if applicable)	GRADE Assessment (if reported)	Publication bias (if reported - method, result)
	HFNC	NIV	Failure of Respiratory Support	Case series	2 studies	Not applicable	Not applicable	Review reported individual rate of intubation per included study Wang K: higher intubation rates in those given HFNC (23/35 [66%]) compared with those on NIV (0/34 [0%]) Wang Y: two (12%) of the 17 patients who received HFNC were intubated while 5 (29%) required NIV as rescue treatment. Only one of the 9 (11%) patients initially given NIV progressed to invasive mechanical ventilation. Authors note: Although failure of initial respiratory support was higher among patients on HFNC compared with NIV in both studies, we cannot conclude about the superiority of HFNC or NIV because of methodological limitations (i.e., retrospective study, no control group, no control for confounders) and potentially unequal groups at baseline.	NR	NR

Author of the SR (Year)	Intervention	Comparator	Outcome	Study design	Number of studies considered for the outcome (with n expressed as total number of participants)	Statistical model (fixed/random effects)	Heterogeneity (I^2 %)	Pooled treatment effect OR any measure reported (expressed as RR, OR, % etc with confidence interval, whenever applicable), p-value, S/NS (if applicable)	GRADE Assessment (if reported)	Publication bias (if reported - method, result)
Quantitative results of included reviews on clinical safety in terms of aerosol generation										
Agarwal et al. (2020)	HFNC	Other NIVs (CPAP)	Distance traveled by respiratory droplets	Simulation study (human patient simulator)	1 study	Not applicable	Not applicable	Increased regions of high aerosol density were noted with increasing flow rates (maximum dimension 6.5 ± 1.5 cm at 10 Lmin-1 to 17.2 ± 3.3 cm at 60 Lmin-1; $p < 0.001$) and increasing positive pressure using CPAP.	NR	NR

Note: RCT: Randomized controlled trial | **OR:** Odds ratio | **RR:** Risk ratio | **MD:** Mean difference | **S:** Statistically significant | **NS:** Not statistically significant | **NR:** Not reported

5.1.1.1.3.3. Critical Appraisal of the included reviews

We performed critical appraisal on the three included SRs in this review using the AMSTAR 2 tool. As for the RR, we devised an adherence checklist based on the Cochrane Rapid Review Interim Guidance with some modifications to align it with the DOH-Health Technology Assessment Unit Methods Guide.

For the included SRs, all were assessed overall to be critically low. Commonly reported critical flaws were failure to explicitly report the following: protocol registration before the commencement of the review, justification for excluding individual studies, consideration of risk of bias when interpreting the results of the review, and assessment of presence and likely impact of publication bias.

On the other hand, the included rapid review (Villanueva, Cruz & Palileo-Villanueva, 2020) adhered to four out of nine items in our devised checklist (i.e., *Study Objectives, Search and Information Sources, Data Extraction,* and *Synthesis of Results*). We note, however, that in the absence of a standard tool for the critical appraisal of rapid reviews, our evaluation does not rate the quality of said review, nor rapid reviews in general.

The critical appraisal of the included reviews can be found in Appendix 5.

5.1.1.2 Review of local studies

5.1.1.2.1. Quantity and characteristics of included local studies

We looked into available local studies on HFNC. Out of the five hospitals we consulted, we noted a study conducted in the Philippine Heart Center. The randomized controlled trial study of See et al. (n.d.) assessed the clinical performance of high-flow oxygen therapy through nasal cannula (HFNC) versus noninvasive positive airway pressure ventilation (NPPV) in non-COVID-19 patients with acute hypoxemic respiratory failure. A total of 96 patients were enrolled in the study. Forty-six patients were assigned to receive HFNC, while 48 patients were assigned to receive NPPV. The primary outcome of the study was treatment failure (defined as need for intubation or invasive mechanical ventilation). The secondary outcomes were length of ICU stay and in-ICU mortality. Other outcomes were reported but are not part of the outcomes of interest include time to intubation and PaO_2: FiO_2 ratio. Mean follow-up time was not mentioned in the study.

Table 7 summarizes the quantity and characteristics of included local study.

Table 7. Characteristics of included local studies

Author of the study (Year)	Characteristics of included local studies					
	Population	**Intervention**	**Comparator**	**Outcome**	**Mean Follow-up Time**	**Study design**
See et al., (n.d.)	N= 94, aged > 19 year old and above referred to pulmonary service with AHRF, who met the following criteria: 1. Respiratory rate > 25 bpm 2. Partial pressure of arterial oxygen (PaO_2) to FiO_2 < 200 mmHg while patient was breathing oxygen flow rate to 10 liters per min or more for at least 15 min. 3. Partial pressure of arterial carbon dioxide ($PaCO_2$) not higher than 45 mmHg 4. Absence of clinical history of underlying chronic respiratory failure such as chronic obstructive pulmonary disease or bronchial asthma	HFNC (Initially set at 50 L/min, subsequent adjustments were made at the discretion of physician)	Non-invasive Positive Pressure Ventilation (NPPV) (i.e., BiPAP)	The reported outcomes were as follows: Primary: treatment failure (defined as need for intubation or invasive mechanical ventilation) Secondary: • Length of ICU stay • In-ICU mortality	Not mentioned	RCT

Notes: **ICU:** Intensive care unit | **RCT:** Randomized controlled trial

5.1.1.2.2. Quantitative synthesis of included local studies

Since we only found one study, we only narratively reported the results. The summary of reported results of the See (n.d.) study is on Table 8.

I. Outcome #1: In-ICU mortality

No significant difference was found for intensive care unit (ICU) mortality with HFNC (n=8, 17.39%) and NPPV (n=14, 29.17%) with p=0.178.

II. Outcome #2: Need for intubation

No significant difference was found for need for intubation with HFNC (n=10, 21.74%) and NPPV (n=12, 25.00%) with p=0.709.

III. Outcome #3: Length of ICU stay

No significant difference was found in length of ICU stay (expressed in hours) with HFNC (2069 hours, 95% CI: 46-2185) and NPPV (2396 hours, 95% CI: 48-2280) with p=0.3738.

Table 8.
Reported findings of the included local studies

Study	Outcome	Treatment arms		p-value
		HFNC (n=46)	NPPV (n=48)	
See (n.d.)	In-ICU mortality	17.39% (8)	29.17% (14)	0.178
	Need for intubation	21.74% (10)	25.0% (12)	0.709
	Length of hospital stay (in hours)	2,069 [46-2185]	2,396 [48-2280]	0.3738

5.1.1.2.3. Critical appraisal of included local studies

We performed critical appraisal on the study of See (n.d.) using Cochrane RoB2 tool. We assessed that they study has low risk of bias on the domains of randomization process, deviations from the intended interventions, and missing outcome data. However, we assessed that the study has a high risk of bias on the domains of the measurement of outcome (i.e., lack of blinding on the part of outcome assessors) and some concerns on the selection of the reported result (i.e., did not indicate a pre-specified analysis plan before unblinded outcome were made available for analysis).

Overall, the study was found to have high risk of bias. The critical appraisal of the See (n.d.) study can be found in Appendix 5.

5.1.1.3. Evidence gathered through expert opinion

This section narrates the expert opinions provided by 12 health professionals who on the use of HFNC for COVID-19. Of these 12 experts, six of whom are pulmonologists, five are respiratory therapists, and a critical care nurse, only six of them provided information on their practice. Majority of the experts (i.e., 5 out of 6) have been in their relevant practice for more than 10 years with majority (i.e., 5 out of 6) having used HFNC for 1 to 14 years. We report the gathered evidence based on submitted written responses, and the discussions during the expert panel consultation. Table 9 summarizes the names and affiliations of the consulted experts.

Table 9.
Names and affiliations of the consulted experts (clinical)

Name of Expert	Specialty	Institution/ Organization
Dr. Guinevere Agra	Pulmonologist	St. Luke's Medical Center – Bonifacio Global City (SLMC – BGC)
Dr. Emily Aventura	Pulmonologist	The Medical City (TMC)
Dr. Jubert Benedicto	Pulmonologist	Philippine General Hospital (PGH)
Dr. Ma. Encarnita Blanco-Limpin	Pulmonologist	Philippine College of Chest Physicians (PCCP), Philippine Society of Critical Care Medicine (PSCCM), Philippine Heart Center (PHC)
Dr. Bernice Ong-Dela Cruz	Pulmonologist	PHC
Dr. Dennis Teo	Pulmonologist	Lung Center of the Philippines (LCP)
Ms. Gemma Barangan	Respiratory Therapist	PHC
Ms. Carole G. Baula	Respiratory Therapist	SLMC – BGC
Mr. Cesar G. Bugaoisan, Jr.	Respiratory Therapist	Association of Respiratory Care Practitioners of the Philippines (ARCPP)
Mr. Joaquin Torres	Respiratory Therapist	PHC
Mr. Wilmer G. Valera	Respiratory Therapist	ARCPP, SLMC – BGC
Mr. Ericson S. Batan	Nurse	Critical Care Nurses Association of the Philippines, Inc. (CCNAPI)

In terms of the place of HFNC in the clinical pathway of COVID-19 treatment, majority of experts agreed that HFNC is used for hypoxemic but not on hypercapnic patients who do not need immediate intubation. Depending on severity, patients are usually started with COT, then shifted to HFNC if the patient does not improve and higher flow rates (>6 L/min) are required. If patient condition continues to deteriorate despite HFNC, intubation is necessary. The panel had varied opinions on which parameter to use for the determination of the need for HFNC. One expert stated that they use the shunt computation while experts from another institution noted that they do not use this parameter due to its difficulty to calculate. They use the simpler P/F ratio instead, wherein a value < 300 warrants the patient as candidate for HFNC therapy.

In terms of escalation to intubation, eight of the twelve experts observed that HFNC can help prevent a patient from proceeding to the more invasive endotracheal intubation. Three experts, on the other hand cited that outcomes on this parameter are inconsistent. The panel emphasized that use of HFNC should not put health care professionals in a "complacent mode". Close monitoring of patient statistics is vital to determine if a patient needs to be intubated. Most of the experts utilize the ROX index to predict the risk of intubation.

Majority of the experts cited that the preference for HFNC is due to its ease-of-use and reported patient comfortability as compared to other interventions. Eight experts stated that patients prefer HFNC because it is noninvasive, and the patients are able to eat and talk without taking off the mask. Three experts added that the heated humidification of HFNC facilitates secretion clearance easily and decrease bronchospasm. For better outcomes, one expert suggested early prone positioning of patient combined with HFNC, but also citing difficulty to maintain a patient in the said position for hours.

With regards to the risk of aerosolization, the expert panel did not recommend the use of other NIVs such as CPAP and BiPAP for COVID-19 patients outside a negative pressure room. Meanwhile, the panel had slightly varied opinions on the risk of aerosolization brought by HFNC. One expert stated that HFNC does not pose the risk of aerosolization, hence, they do not require a negative pressure room in their hospital. Meanwhile, two experts stated that HFNC has a relatively lower risk of aerosolization compared to other NIVs. One of them mentioned that HFNC has decreased aerosol density, as long as flow is limited to less than 30L/min. Three experts, on the other hand, noted that HFNC manifests the risk of aerosolization thus, they recommend it to be done with a negative pressure HVAC system or a single room if the said technology is unavailable.

For the oxygen flow rates, one expert stated that they limit it to 40L/min when using HFNC, citing that beyond this flow rate, there might already be delayed intubation, and "tired" patients may start to experience ventilatory failure. The same expert cited that in the US, they use 60 L/min as limit. However, higher flow rates are more expensive since it means more oxygen consumption. One expert added that higher/modern versions of mechanical ventilators capable of delivering high-flow rates like HFNC are also being utilized in some hospitals. However, another expert clarified that while these mechanical ventilators can also humidify air, HFNC provides better humidification.

In terms of logistics, two experts stated that HFNC kits are preferably requisitioned together with a flow meter that are capable of delivering high flow rates up to 60-70 L/min. The device also requires a wall-mounted oxygen port because they are not compatible for mounting on oxygen tanks.

Lastly, in terms of adverse events, majority of experts agreed that serious adverse events such as barotrauma and ventilator-associated pneumonia are observed more on patients hooked to mechanical ventilators as compared to patients on non-invasive strategies such as HFNC. Thus, higher level of monitoring is required for patients on mechanical ventilation.

To supplement the current available evidence, there are four local hospitals (i.e., PGH, PHC, SLMC, LCP) that are conducting studies on the use of the HFNC for COVID-19. The results are expected to be out later this year or early next year.

The discussions per question are detailed in Table 10.

Table 10.
Key discussions from submitted written responses and expert panel consultation (clinical)

Question	Aligned discussion points	Discussion points with varying opinions
In the current COVID-19 pathway, when is HFNC used? Some points to consider: • Population whom HFNC is used (e.g., patients with AHRF) • Criteria on qualifying a patient to receive HFNC • Treatment guidelines being followed	***Population whom HFNC is used and criteria on qualifying a patient to receive HFNC*** Inputs from pulmonologists: • HFNC may be used when a patient is on low flow oxygen supplement yet has oxygen saturation (SpO_2) of less than 93% and/or continues to be dyspneic or tachypneic. **(1 of 6 pulmonologists)** • If a patient is hypoxemic, oxygen supplementation (regular nasal cannula) is usually provided with a flow rate of 6 L/min. **(3 of 6 pulmonologists)** Traditional face masks can also be used since a regular nasal cannula can only provide FiO_2 at 45%. **(2 of 6 pulmonologists)** However, traditional facemasks have higher leakage and risk for aerosolization. If the patient remains hypoxemic, the patient is moved to HFNC therapy instead. **(3 of 6 pulmonologists)** • In terms of sequence, regular nasal cannula is used first, then the rebreathing mask. HFNC is then used if the patient stats are not improving. **(2 of 6 pulmonologists)** • It also depends on the severity of COVID-19 condition. If patients improve after a week of HFNC therapy, they are shifted to regular nasal cannula. If there is a need to re-escalate the oxygenation technique, the transition of treatment from "COT to HFNC" is easier than "COT to other NIVs." Transition from "COT to mechanical ventilation" is a lot harder when	***The use of shunt computation to determine if a patient is eligible to receive HFNC therapy*** The discussion was on the use of shunt computation to determine if a patient is candidate for HFNC therapy. One expert mentioned that when hypoxemia is between 30-40% based on the shunt computation, they observed that HFNC therapy is more successful in these percentages. Further, they have a chart correlating P/F ratio and FiO_2 with shunt computation. However, two of six pulmonologists expressed that they do not use the shunt computation owing to its difficulty to calculate. Instead, they use the use O_2 saturation, respiratory rate, or P/F ratio as parameters. Particularly, if the P/F ratio is < 300, these patients are candidates for HFNC therapy. ***Mechanical ventilators with high-flow rates feature similar to HFNC*** One expert mentioned that higher/modern versions of mechanical ventilators are capable

Question	Aligned discussion points	Discussion points with varying opinions
	compared to transition to HFNC or other NIVs. **(2 of 6 pulmonologists)** Inputs from respiratory therapists: • The primary strategy for COVID 19 is supportive care including oxygen therapy using HFNC. HFNC is indicated for patients with moderate to severe respiratory distress despite COT, and continuing hypoxemia (SpO_2< 90%). It can also be used in patients with mild respiratory distress to prevent further deterioration. **(3 of 5 respiratory therapists)** Inputs across specialties: • HFNC is used to patients with increasing oxygen requirement, to reduce work of breathing, and lessen the need for invasive oxygen support [i.e., intubation]. **(8 of 12 experts)** ***Treatment guidelines*** • We use the guidelines from PCCP- PSMID-PCP (as of July 20, 2020). **(5 of 12 experts)** • The use of HFNC as part of treatment guidelines is still "murky." A retrospective study on HFNC is being conducted at LCP. It will be out later this year or early next year. **(1 of 12 experts)**	of delivering high-flow rates like HFNC; hence, some hospitals are maximizing this feature. However, another expert clarified that HFNC is capable of better humidification than these mechanical ventilators.

Question	Aligned discussion points	Discussion points with varying opinions
What is your experience on the use of HFNC for COVID-19 patients with acute hypoxemic respiratory failure (AHRF)? *Some points to consider:* • *Observable change in a) mortality rates; b) escalation to intubation; c) hospital length of stay; d) ICU length of stay*	***HFNC versus other NIVs*** • HFNC does not aerosolize which makes it less risky for healthcare workers. **(1 of 12 experts)** • As compared to BiPAP, HFNC decreases risk of airborne transmission due to decreased aerosol density (as long as flow is limited to less than 30L/min). **(1 of 12 experts)** • Due to increased aerosolization of droplets, experts do not recommend BiPAP or CPAP for COVID-19 patients, unless it can be done in a room equipped with a negative pressure HVAC system. **(2 of 12 experts)** • In providing HFNC to COVID 19, additional infection control measures should be employed wearing surgical mask over the cannula and admitting the patient in a negative room [or a single room if not available] to prevent the health workers from the risk of aerosolization. **(3 of 12 experts)** **<u>Other points</u>** • The HFNC therapy is significantly appreciated by patients. **(1 of 12 experts)** • One expert noted that they still need to look closely at their data for the actual figures. Outcomes cannot be correlated to HFNC use alone since other interventions are also being administered to the patients. • For the flow rate of HFNC has a set limit of 40 L/min. Beyond that, there might be a delay to those patients who would need intubation, and patients start to experience ventilatory failure for some patients who are already "tired." In the US, they use	None

Question	Aligned discussion points	Discussion points with varying opinions
	60 L/min but it is more expensive since higher flow rate means higher oxygen consumption. **(1 of 12 experts**	
Is there a preference to use HFNC over other non-invasive therapies (e.g., other NIVs) or invasive/mechanical ventilation? Kindly justify.	***On the use of HFNC*** • HFNC is used for hypoxemic patients as other NIVS are poorly tolerated. **(4 of 12 experts)** • For patients with hypoxemic respiratory failure, it is preferred to use HFNC. **(7 of 12 experts)** • HFNC is easy to use. **(4 of 12 experts)** • Non-invasiveness of HFNC causes lesser anxiety to patients as compared to MV through endotracheal tube. **(8 of 12 experts)** • HFNC is more comfortable, patients can eat and talk without taking off mask; and the patients are easier to prone [compared to other NIVs]. **(8 of 12 experts)** • The heated humidification of HFNC facilitates secretion clearance easily and decrease bronchospasm. **(3 of 12 experts)** • HFNC is being maximized to the fullest before opting to use invasive mechanical ventilation. **(1 of 12 experts)** • However, the use of HFNC can put a healthcare professional in "complacent mode"; hence, there is a delayed realization that a patient already needs to be intubated. **(4 of 12 experts)** ***On the use of other NIVs*** • For patients with COPD or mild hypoxemia, BiPAP or other NIVs are used. **(1 of 12 experts)** • Other NIVs are used for hypercapnic respiratory failure. **(4 of 12 experts)**	None

Question	Aligned discussion points	Discussion points with varying opinions
	• The pressure build- up by other NIVs brings patient discomfort and may be poorly tolerated and even frightening for some patients due to the high pressures delivered in the airways, difficulty in synchronizing breathing, claustrophobia, stomach distention and mask- related side effects. **(3 of 12 experts)** • Other NIVs are potentially aerosol-generating procedures and therefore should NOT be used routinely among COVID-19 patients. **(1 of 12 experts)** ***On the use of mechanical ventilators*** • The problem on the use of mechanical ventilators is its invasiveness. Patients usually prefer non-invasive treatments. • If patient conditions continue to deteriorate based on ROX index, despite non-invasive oxygenation strategies, intubation is necessary. **(7 of 12 experts)**	
Are you aware of a local study (published or unpublished, observational or RCT) that demonstrated the relative treatment effects of HFNC compared to COT or other NIVs for COVID-19 patients with AHRF? Are you aware of any other sources of data that assessed the clinical performance of HFNC versus COT or other NIVs for COVID-19 patients with AHRF?	Four local hospitals have ongoing studies regarding the use of HFNC on COVID-19 patients: • Ongoing study at SLMC-BGC • Ongoing retrospective study at LCP, data to be available this year or early next year • Ongoing study at PGH, data to be available on January 2021 • Ongoing retrospective study at PHC, data to be available this year	None

Question	Aligned discussion points	Discussion points with varying opinions
Does the use of the following health technologies cause any foreseeable side effects and/or adverse effects (AEs)? What are these side effects and/or AEs? Do they require preventive management, monitoring or additional treatment cost? Technologies: • HFNC • Other NIVs • Invasive mechanical ventilation	*This question was primarily addressed by the six pulmonologists in the panel.* **HFNC** • Gastric distension (less common) **(4 of 6 pulmonologists)** • Eye irritation **(4 of 6 pulmonologists)** • Epistaxis **(4 of 6 pulmonologists)** • Nasal irritation **(4 of 6 pulmonologists)** • Trauma **(4 of 6 pulmonologists)** • Intolerance to the temperature of the humidifying fluid (heat increases as the humidifying fluid dries up); hence, there is a need to constantly monitor the amount of water in HFNC to regulate the temperature **(4 of 6 pulmonologists)** • Clogging of prongs due to secretions **(4 of 6 pulmonologists)** • In terms of preventive management, only minimal management is required. **(1 of 6 pulmonologists)** **Other NIVs** • Abdominal bloating (gastric distention) **(4 of 6 pulmonologists)** • Facial skin erosion due to constant pressure on the face of the patient **(4 of 6 pulmonologists)** • Discomfort and pain in the sinus and ears as well as pressure sores from constant trauma. **(4 of 6 pulmonologists)** • Hypotension **(4 of 6 pulmonologists)** • Nasal or oral dryness **(4 of 6 pulmonologists)** • Aspiration pneumonia **(4 of 6 pulmonologists)** • In terms of preventive management, minimal to moderate management is required. **(1 of 6 pulmonologists)**	**HFNC-associated pneumomediastinum** According to one expert, some case reports on COVID-19 patients reported cases of pneumomediastinum associated with the use of HFNC High HFNC flow rates of 60 LPM was suspected. Hence, 40 L/min is used (a more conservative flow rate) since there is uncertainty on the effect of HFNC. However, one expert mentioned that they did not observe occurrence of pneumomediastinum associated with the use of HFNC on patients admitted in their facility.

Question	Aligned discussion points	Discussion points with varying opinions
	Invasive ventilation • Ventilator-associated pneumonia **(4 of 6 pulmonologists)** • High number of patients who develop barotrauma (pneumothorax) **(4 of 6 pulmonologists)** • Prone to subcutaneous emphysema **(4 of 6 pulmonologists)** • Pneumomediastinum **(4 of 6 pulmonologists)** • Ventilator associated lung injury **(4 of 6 pulmonologists)** • Gastric disturbances (motility) **(4 of 6 pulmonologists)** • In terms of preventive management, regular management is required. **(1 of 6 pulmonologists)**	
Is there any information that you would like to be considered in the assessment of HFNC for COVID-19 patients with AHRF?	• Patients are placed in awake prone positioning. However, it is difficult to maintain them in this position, particularly for elderly even if we modify the prone position. It is a challenge to sustain a patient in this position for 12-16 hrs. If the patient remains hypoxemic under COT, they are shifted to HFNC (still in a prone position). It is really to avoid them to proceed to mechanical ventilation (MV). In the US, patients in MV reported a high rate of mortality MV should be avoided. **(4 of 12 experts)** • In terms of logistics, HFNC should be procured together with a flow meter with about 60-70 L/min flow rate. Since some suppliers sell it without a flow meter, then it has to be procured separately. **(2 of 12 experts)** One of them added that they use the available flow meters with lower ranges as alternative. They found out	None

Question	Aligned discussion points	Discussion points with varying opinions
	that sometimes wall-mounted oxygen can still deliver flow rates higher than what can be read by the flow meter. **(1 of 12 experts)** • Oxygen source should be wall-mounted. **(2 of 12 experts)** • Early intubation can be considered if patient is worsening. **(3 of 12 experts)**	

Two local experts also provided their institutional guidelines on the use of HFNC. The following table compares the use of HFNC from the HPAAC Unified Algorithm (as of November 7, 2020), with institutional guidelines of the Lung Center of the Philippines (LCP) and Philippine Heart Center (PHC) (Table 11) on the management of AHRF among COVID-19 patients.

We noted that in the HPAAC and PHC guidelines, both mentioned specific patient statistics when to initiate HFNC therapy. The LCP and PHC guidelines explicitly stated that HFNC is indicated for patients with AHRF (Type I Acute Respiratory Failure). The guidelines of LCP and HPAAC both mentioned the need for a negative pressure room when administering HFNC. According to LCP, if negative pressurized room is not available, HFNC can be used in single room if used for COVID-19 or other respiratory infectious diseases. Further, all three guidelines used the ROX index at nearly the same cutoff values to predict the risk for intubation. Only the institutional guideline of LCP mentioned when HFNC is contraindicated, as well as de-escalation algorithms, weaning and other step-down strategies of respiratory support (i.e., COT).

Table 11.
Comparison of local guidelines

Parameter	HPAAC Unified Algorithm (as of November 7, 2020)	Institutional guideline of LCP (n.d.)	Institutional guideline of PHC (n.d.)
Indication/When to initiate HFNC	Management of ARDS Start oxygen support therapy for adult patients with COVID pneumonia with respiratory symptoms or distress with following patient statistics:	HFNC can be used on the following: • Type I Acute Respiratory Failure (less than 40% shunt) • Type 3 Acute Respiratory Failure with no significant risk for hypercapnia	Respiratory Support Algorithm in COVID-19 Pneumonia with Acute Hypoxemic Respiratory Failure

Parameter	HPAAC Unified Algorithm (as of November 7, 2020)	Institutional guideline of LCP (n.d.)	Institutional guideline of PHC (n.d.)
	• Respiratory rate > 30 OR • Peripheral capillary oxygen saturation < 92% OR • Systolic blood pressure < 90 Options for Oxygen support therapy are: 1. Face mask or non-rebreather mask with HEPA filter. 2. High flow nasal cannula (HFNC) at 40-60 L/min overlapped with a face mask 3. Non-invasive positive pressure ventilation. Oxygen saturation should be maintained at >92%.	• Pneumonia (CAP, SARS and other Severe Acute Respiratory Infection) • Pneumothorax • Compensated Interstitial lung disease • Mild Type 2 Acute respiratory failure (compensated) • Post weaning and extubation bridging • Non intubated patients requiring high flow oxygen while doing bronchoscopy procedure • End of life (relative indication) • Compensated Heart failure with hypoxemia not requiring PEEP or positive pressure breathing	If the patient statistics are as follows even after administration of 6 L/min COT: • PaO2 < 70 mm Hg with O_2 • PaO2/FiO2 = 200-300 • RR < 30/min Place patient on HFNC. If HFNC is not available, place on NIV. Re-evaluate after 1-2 hours.
Precautions	May use high flow nasal cannula at 40-60 L/min overlapped with a face mask or non-invasive positive pressure ventilation in a single negative pressure room.	For COVID-19 patients, HFNC is not recommended for use in the ICU without negative pressure HVAC system as aerosolization can spread the virus to other patients. If in a single room, it is advised that patients still wear a surgical mask and a mask can cover the exhalation port of the HFNC. The health workers	Not mentioned

Parameter	HPAAC Unified Algorithm (as of November 7, 2020)	Institutional guideline of LCP (n.d.)	Institutional guideline of PHC (n.d.)
		caring for the patients are advised to wear PPE at all times.	
Contraindication	Not mentioned	<u>Absolute</u> • Consciousness disorder (no response, agitated) • Uncooperative • Airway obstruction • Abnormalities or surgery of the face, nose, or airway that preclude an appropriate-fitting nasal cannula • Copious sputum • Risk of aspiration • Unstable hemodynamics (shock, intractable arrhythmia, post-CPR, respiratory arrest) • Moderate to severe Type 2 Acute respiratory failure Relative: • Shunt fraction >40% • P/F < 150 • Some experts avoid HFNC in those following upper airway surgery to avoid the theoretical risk that the high pressure may precipitate a venous thromboembolism	Not mentioned
Monitoring/ Escalation to intubation	Monitor changes in sensorium, hemodynamics, EKG changes, respiratory rate, and O_2 saturation.	Monitoring of patients on High flow Nasal Cannula, would be mainly be divided into two main parts: clinical monitoring of sensorium, respiratory effort and cardiovascular status (heart	Re-evaluate after 1-2 hours after administration of HFNC therapy.

<table>
<tr><th>Parameter</th><th>HPAAC Unified Algorithm (as of November 7, 2020)</th><th>Institutional guideline of LCP (n.d.)</th><th>Institutional guideline of PHC (n.d.)</th></tr>
<tr><td></td><td>Perform intubation if the ROX index are less than these values at the hours of checking:
2 hours - <2.8
4 hours - <3.47
12 hours - <3.85</td><td>rate and blood pressure). The second is ROX index which is SPO2/FiO2% divided by respiratory rate per minute.

The ROX index is monitored at 0 hour, two hours, 6 hours and 12 hours. A value of greater than 4.88 would mean success of therapy. The first day is crucial as to the decision of shifting the patient to another modality such as intubation.

<table><tr><th>Hours of HFNC use</th><th>ROX index for failure</th></tr><tr><td>2</td><td>< 2.85</td></tr><tr><td>6</td><td>< 3.47</td></tr><tr><td>12</td><td>< 3.85</td></tr><tr><td>>12</td><td>< 4.88</td></tr></table></td><td>If the patient statistics are as follows:
SaO2 < 92%
RR > 30/min
PaO2/FiO2 < 200
ROX<2.85, 3.47 & 3.85 at 2, 6, 12 hrs
Progression of infiltrates on CXR
Intubate the patient if no “Do not intubate (DNI)” order. Otherwise, if the patient statistics improve, continue HFNC therapy and re-evaluate after 1-2 hours and as needed.</td></tr>
<tr><td>De-escalation</td><td>Not mentioned</td><td>The principle of de-escalation treatment from high flow nasal cannula, is clinical improvement, regression of chest x-ray infiltrates and a ROX index of greater than 4.88 even with the lowering of the FiO_2 and flow rates. There are different ways of lowering but we alternately lower the FiO_2 and flow rates every hour. Once patient tolerates FiO_2 of less than 30% and flow rates of less than 20 L/min, they can be shifted to a non-rebreather mask or a regular nasal cannula.</td><td>Not mentioned</td></tr>
</table>

5.1.2. Review of clinical guidelines and existing findings and recommendation from HTA agencies on the use of HFNC

5.1.2.1. COVID-19 treatment guidelines of organizations or countries on the use of HFNC

Of the 15 countries/organizations reviewed for treatment guidelines on the use of HFNC, 11 (WHO, the Philippines, Australia, Canada, China, Indonesia, Japan, Malaysia, UK, US, and Vietnam) have mentioned the use of HFNC in their guidelines; three (Singapore, South Korea, and European CDC) did not mention HFNC in their guidelines, and one (Thailand) was not accessible. Indonesian, Japanese, and Vietnamese guidelines were translated to the English language using Google translate.

In terms of the nature of recommendations on the use of HFNC, four guidelines (China, Philippines, US, and Vietnam) have provided solely positive recommendations but with conditions for use; one guideline (UK) has provided a negative recommendation; and, six guidelines (WHO, Canada, Indonesia, Japan, Australia, Malaysia) have provided conditions for use where HFNC is positively or negatively recommended.

In terms of the applicability of recommendations based on age, seven guidelines (WHO, Canada, Indonesia, Japan, China, Australia, Vietnam) have provided recommendations regardless if adult or pediatric population; one guideline (Malaysia) has provided separate recommendations for adult and pediatric population; and, three guidelines [Philippines, US, UK (England)] have provided recommendations only for adult population.

Of those with positive recommendations on the use of HFNC for COVID-19 patients, the following are the conditions for use:

- Selected COVID-19 patients with mild ARDS may be given a trial of HFNC or NIV. However, patients receiving a trial must be monitored closely and cared for by personnel experienced with HFNC or NIV. In the event that the patient acutely deteriorates or does not improve after a short trial of about 1 hour, intubation should not be delayed. Evaluation of oxygen capacity of the patient should be done if HFNC or NIV will be used outside of usual care settings *(WHO, Canada and Indonesia - level of recommendation per organization or country not indicated)*
- In the event a patient will be intubated, pre-oxygenation (FiO_2 of 100% for 5 minutes) may be done via facemask with airbag, bag-valve mask, HFNC, or NIV *(Indonesia - level of recommendation not indicated)*
- May be given when respiratory distress and/or hypoxemia of the patient cannot be alleviated after receiving COT *(US - moderate recommendation; China, Vietnam - level of recommendation not indicated).* In patients who do not improve with COT, or with PaO_2/FiO_2 ratio of < 200 mmHg, HFNC is performed. *(China – level of recommendation not indicated).* If conditions do not improve despite giving HFNC, intubation must be not be delayed. *(US – level of recommendation not indicated).* Shifting from COT to HFNC, or HFNC to intubation is indicated if conditions do not improve after 1-2 hours. *(China – level of recommendation not indicated)*.
- Prone positioning for >12 hours should be performed in HFNC patients if not contraindicated *(China- level of recommendation not indicated).*
- HFNC may be considered for patients with SpO_2 ≤93% even after O_2 administration, steroids, or remdesivir (also classified as moderate II patients with respiratory failure). It must be set to 30 - 40 L / min. *(Japan– level of recommendation not indicated)*

- If the pediatric patient is still hypoxic despite low-flow nasal cannula (LFNC), HFNC can be used, but limit it preferably in negative pressure isolation room (since use of HFNC is considered aerosol generating procedure) *(Malaysia – level of recommendation not indicated)*
- If the option is to use HFNC on a patient it should be and done in a single negative pressure room with the healthcare worker wearing complete personal protective equipment (PPE). *(WHO, Philippines, Australia, Canada, and Japan – level of recommendation per organization or country not indicated).* If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only *(WHO, Australia and Canada – level of recommendation per organization or country not indicated).*
- The option to use HNFC should also be done with a surgical mask. *(Philippines and Japan – level of recommendation per country not indicated.)*
- HFNC may be used at 40-60L/min overlapped with face mask and NIPPV in a single negative pressure room, for adult patients with respiratory symptoms or distress (RR>30, peripheral capillary oxygen saturation < 92%, or systolic blood pressure < 90). Along with HFNC, other options include the use of facemask or non-rebreather mask. *(Philippines – level of recommendation not indicated).*

In summary, of the ten guidelines that indicated positive recommendations for HFNC use, seven has recommended it for patients in respiratory distress and/or hypoxemia. Six of these seven guidelines recommended it as a next step after failure in COT. Meanwhile, the other three guidelines (WHO, Canada, Indonesia) recommended it only for mild ARDS. In addition, six of the ten guidelines also mentioned the preference on using HFNC in a negative pressure room.

On the other hand, for those with negative recommendations on the use of HFNC, the following are the reasons or circumstances for it rejection in the guidelines:

- HFNC or non-invasive positive pressure ventilation (NIPPV) are not recommended due to risk of environmental pollution but can be considered for patients with severity classification of moderate II with respiratory failure. *(Japan – level of recommendation not indicated)*
- NIV is generally discouraged in the management of COVID-19 among adult patients (*Malaysia – level of recommendation not indicated*).
- HFNC is advised not to be used as local maximum outlet delivery limitation preclude widespread use and the uncertainty on the risk of environmental viral contamination but this may be higher in HFNC than in invasive mechanical ventilation (*UK – level of recommendation not indicated*).
- HFNC is also not recommended for use among patients with hypoxemic respiratory failure and hemodynamic instability, multiorgan failure or abnormal mental status (*WHO, Canada and Indonesia – level of recommendation per organization or country not indicated*).
- HFNC should not be given in shared wards, emergency department cubicles or during inter-hospital patient transfer/ retrieval (*Australia – level of recommendation not indicated*).

To sum it up, seven guidelines gave conditions for negative recommendations. Three of these guidelines did not recommend it for patients with hypoxemic respiratory failure. One did not recommend it for pediatric patients. Two did not recommend it due to risk of environmental contamination with one also citing limited supply of the technology. Lastly, one guideline did not recommend it for use in shared spaces and during patient transfers.

The COVID-19 treatment guidelines of organizations or countries on the use of HFNC is tabulated in Appendix 6.

5.1.2.2. Review of existing findings and recommendations of different HTA agencies on the use of HFNC

None of the 13 HTA agencies reviewed has completed an assessment on the use of HFNC for COVID-19 patients with AHRF.

5.2. Resource requirements and costing of HFNC

This section details the expert opinions of health professionals, and responses of representatives from selected private and public hospitals, and selected DOH offices on the resources required for the use of HFNC compared to other NIVs for COVID-19 patients with AHRF. We note that we received responses from the DOH-Health Facilities and Services Regulatory Bureau (HFSRB) and DOH-Health Facilities Development Bureau (HFDB) and guidance to forward our queries to DOH-Health Facilities Enhancement Program (HFEP). We report the gathered evidence based on submitted written responses, and the discussions during the expert panel consultation. Names and affiliations of health professionals consulted can be seen in Table 12.

Table 12.
Names and affiliations of the consulted experts (resource requirements and costs)

Name of Expert	Specialty	Institution/Organization
Dr. Joel Abanilla	Cardiologist	Philippine Heart Center (PHC)
Dr. May Agno	Pulmonologist	The Medical City (TMC)
Dr. Emily Aventura	Pulmonologist	TMC
Dr. Jubert Benedicto	Pulmonologist	Philippine General Hospital (PGH)
Dr. Ma. Encarnita Blanco-Limpin	Pulmonologist	Philippine College of Chest Physicians (PCCP), Philippine Society of Critical Care Medicine (PSCCM), Philippine Heart Center (PHC)
Dr. Bernice Ong-Dela Cruz	Pulmonologist	PHC
Dr. Dennis Teo	Pulmonologist	Lung Center of the Philippines (LCP)
Ms. Gemma Barangan	Respiratory Therapist	PHC
Mr. Joaquin Torres	Respiratory Therapist	PHC
Dr. Leonita P. Gorgolon	-	Director IV, DOH – Health Facilities Enhancement Program
Representative, Office of the Executive Vice President and Chief Medical Officer	-	St. Luke's Medical Center – Bonifacio Global City (SLMC)

Based on the feedback of experts, there are no significant additional personnel required and changes in their roles in the use of HFNC versus other NIVs. Both HFNC and other NIVs would require the support of a pulmonologist, a respiratory therapist, and a nurse. Minimal training on the use of HFNC and other NIVs may be required especially on the use of the machines.

There are no necessary preparations prior to administration of HFNC besides attaching the high flow nasal cannula to the patient. For other NIVs, the only preparation done prior to initiation of the procedure is ensuring that the NIV mask is comfortably fitted to the patient's face and that there are no leaks.

As for the medical equipment, the hospitals, represented by the consulted experts answered that they have the necessary medical equipment for performing HFNC and NIV for patient management. As with infrastructure requirements, because there is concern that HFNC poses a risk for aerosol generation, using HFNC requires that the patient be in a single room with a negative pressure HVAC system to ensure that transmission of the infection is minimized. However, one hospital, which does not have negative pressure rooms, maintains that these special rooms are not required for HFNC. Using other NIVs also poses an increased risk of aerosol generation; hence, oxygen therapy needs to be conducted in a negative pressure room. One of the clinical experts consulted said that other NIVs do not need any special room but is preferably done in the ICU. Both procedures require an oxygen gauge and sufficient oxygen supply but according to two experts, HFNC requires that the oxygen source be wall-mounted, and not from a tank. However, one expert said that HFNC can be operated by simply connecting the machine to an electrical outlet and to an oxygen supply which can come from a standard oxygen cylinder or from an oxygen piping system. Further, one of the infrastructure limitations of HFNC is that it is not portable because it does not have battery capability.

While both HFNC and other NIVs require consumables including disinfection materials and PPE, there is an additional consideration that two experts emphasized on regarding the added costs for HFNC due to the reported poor quality of some consumables. The quality of the accessories and peripherals needed for HFNC vary for each brand and some hospitals have observed deterioration in the accessories such that new kits, packs or tubes would have to be opened, at cost.

The consolidated answers of the expert panel on the resources required for the use of HFNC and other NIVs can be seen in Table 13.

Table 13.
Resource requirements of HFNC compared to other NIVs

Requirement	HFNC	Other NIVs
Personnel	Requires the pulmonologist, respiratory therapist, and nurse. (1 out of 11 experts) The pulmonologist shall oversee the FiO2 and flow rate during hookup, monitor, and discontinue HFNC. (2 out of 11 experts) The respiratory therapist is also in charge of monitoring especially during desaturation of O2 and	Requires the pulmonologist, respiratory therapist, and nurse. (2 out of 11 experts) No significant change in personnel and tasks but at least a respiratory therapist or doctor should be in charge of hook-up and monitoring. (2 out of 11 experts)

Requirement	HFNC	Other NIVs
	loosening of the nasal cannula. (1 out of 11 experts) The nurse shall perform the hookup. (1 out of 11 experts)	
Training of personnel	Minimal training required. (2 out of 11 experts) Respiratory therapist must be trained on the set-up, calibration and disinfection of the machine. (1 out of 11 experts) Pulmonologist may need training on machine settings. (1 out of 11 experts)	Minimal training required. (2 out of 11 experts) Respiratory therapist must be trained on the use, titration and disinfection of the machine. (1 out of 11 experts) Pulmonologist may need training on the indications and discontinuation of use. (1 out of 11 experts)
Consumables	1) Heated tube and autofill chamber kit 2) Nasal cannula 3) Sterile water 4) Sterile mask 5) Disinfection materials 6) Personal protective equipment (PPE) 7) Ultraviolet light 8) Humidifier The quality of the accessories for the set-up of HFNC varies for each brand. Additional costs are seen when new kits and tubing are needed due to poor quality accessories. (2 out of 11 experts)	1) BiPAP/CPAP breathing circuit 2) BiPAP/CPAP filter 3) Silicone NIV mask 4) Heat and moisture exchanger (HME) filter 5) Disinfection materials 6) Personal protective equipment (PPE) 7) Ultraviolet light 8) Sterile water 9) Flow sensor 10) Humidifier
Preparation prior to initiation of HFNC	Attaching the high flow nasal cannula to the patient. (1 out of 11 experts)	Fitting of the NIV mask to ensure patient comfort and to secure the mask such that there are no leaks. Pressure adjustments are performed immediately after hooking the patient to the machine. (2 out of 11 experts)
Administrative concerns	Hospitals have the HFNC machines needed for the health technology.	Mechanical ventilators are capable of NIV.
Infrastructure	Isolated room with negative pressure. (2 out of 11 experts) However, one hospital maintains that a negative pressure room is not required for HFNC.	Negative pressure room. (1 out of 11 experts) No special room is required but the ICU is preferred. (1 out of 11 experts)

Requirement	HFNC	Other NIVs
	Minimal storage space needed. Oxygen gauge and sufficient oxygen source are needed. (1 out of 11 experts) The oxygen source must be wall-mounted. HFNC also requires a flow meter to be purchased separately since HFNC machines do not come with a flow meter. (1 out of 11 experts) However, one expert said that the oxygen supply can come from either a standard oxygen cylinder or from an oxygen piping system. (1 out of 11 experts) HFNC is not portable because it is not battery-capable. (1 out of 11 experts)	Minimal storage space needed. (1 out of 11 experts) Oxygen gauge and sufficient oxygen source are needed. (1 out of 11 experts)

As for the associated costs, daily costs on top of the machine set-up costs were derived based on the data provided by the selected health facilities. The patient using either HFNC or other NIVs shall be charged the initial set-up cost and daily costs for oxygen consumption, rental for the machine use, and consumption of sterile water for injection (SWFI). The initial set-up cost for HFNC in two hospitals includes the cannula, tube, and chamber kit, while one hospital has also included the machine usage for 24 hours and two bottles of sterile water in their initial package. On the other hand, initial set-up cost for other NIVs includes the mask and breathing circuit. With both treatment modalities, the patient would have to pay for the daily oxygen consumption. The cost of oxygen consumption depends on the flow rate or FiO2 ordered by the pulmonologist which shall also depend on the severity of the patient's case. In one public hospital, patients using HFNC with flow rates greater than 10L/min will still be charged the same rate for oxygen use at 9-10L/min. An additional cost to a patient using other NIVs is the cost for the HEPA filter that shall be replaced every two to three days. While the data on initial set-up and daily costs are available, direct comparison of the cost of HFNC compared to other NIVs is not feasible because of the data gaps on the average duration of usage of both treatment modalities and on the daily oxygen consumption used in different patient cases. The initial and daily costs associated with HFNC and other NIVs are summarized in Table 14.

Table 14.
Projected initial and daily costs of HFNC compared to other NIVs

Cost Items	HFNC	Other NIVs
Initial set-up	Php 10,000.00 – 13,000.00	Php 6,754.00 - 14,549.25
Daily Oxygen consumption	Php 95.00* per hour Php 2,280.00 for 24 hours	Php 30.00 - 95.00 per hour Php 720.00 - 2,280.00 for 24 hours
Daily rate for machine use	Php 1,100.00 - 2.030.00	Php 1,840.00 - 2,860.00
Daily SWFI consumption	Php 164.00 - 358.00	Php 82.00 - 179.00
HEPA Filter	N/A	Php 222.00 - 256.00 (to be replaced every two to three days)

*In one public hospital, patients using HFNC with flow rates greater than 10L/min will still be charged the maximum hourly rate for oxygen consumption, which is Php 95.00 per hour.

In terms of health systems impact, administering either of the health technologies will incur little to no organizational change, aside from the special infection control procedures specifically for COVID-19. However, one expert noted that hospitals using HFNC may need to hire additional respiratory therapists. The use of any of the health technologies requires minimal training. Health facility-wise, the use of HFNC and other NIVs for COVID-19 patients should be done in separate wards. One expert emphasized that other NIVs may only be used for COVID-19 if an isolated room or a room with negative pressure may be provided. When asked about conversion of the health technologies for respiratory support from non-COVID to COVID-19 use, one expert said that HFNC and other NIVs are quite adaptable. On the other hand, one expert said that within their hospital, essentially all HFNC units may need to be converted for COVID-19 use but other NIVs may not be suitable for use among COVID-19 patients. One expert also noted that considering conversion of provincial hospitals to accommodate patients for use of HFNC may be necessary, but this is depending on the presence of wall-mounted oxygen and a pulmonologist. Finally, concerns that the respiratory interventions may produce aerosols during use must be addressed for both HFNC and other NIVs.

Table 15.
Health systems impact of HFNC compared to other NIVs

Requirement	HFNC	Other NIVs
Organizational changes	No change (2 out of 11 experts) In some cases, there may be a need to hire additional respiratory therapists (1 out of 11 experts) Yes (1 out of 11 experts)	No change (2 out of 11 experts) Yes (1 out of 11 experts)
Training of health facility end users	Minimal training (3 out of 11 experts)	Minimal training (3 out of 11 experts)
Additional changes in the health facility if HFNC is used for COVID-19	Separate wards, single occupancy, additional PPE and disinfection (2 out of 11 experts)	Separate wards, single occupancy, additional PPE and disinfection (2 out of 11 experts)

Requirement	HFNC	Other NIVs
	Generally recommended for COVID-19 (1 out of 11 experts)	Only used for COVID-19 if an isolated room or one with negative pressure is provided (1 out of 11 experts)
Conversion of health facilities from non-COVID to COVID-19 use	Consider conversion of provincial hospitals to accommodate patients for use of HFNC. It depends on the presence of wall-mounted O2. We acknowledge that the majority of the hospitals will not have the wall-mounted O2. Also, not all physicians are knowledgeable on handling HFNC. It needs to be a pulmonologist. (1 out of 11 experts) Essentially all may need to be converted (1 out of 11 experts) Quite adaptable (1 out of 11 experts)	Quite adaptable (1 out of 11 experts) Not used for COVID in their hospital (1 out of 11 experts)
Other resource needs	Concern for aerosol generating procedure (1 out of 11 experts)	Concern for aerosol generating procedure (1 out of 11 experts)

5.3. Ethical and social assessment of HFNC

To assess the ethical and social implications of HFNC, two methods were employed, namely an online survey (using Google Forms) and small group discussion. Four patient groups were invited to participate in the assessment, however, only three of these sent their representatives. These three patient group representatives are from different patient organizations: Philippine Alliance of Patient Organizations (PAPO), New Vois Association of the Philippines, and National Council on Disability Affairs (NCDA). While all three informants participated in the small group discussion, only one responded in the online survey. Only one informant sent an accomplished informed consent form. Verbal informed consent was elicited from all three informants prior to the SGD.

5.3.1 Google Forms survey

Based on the online survey conducted, the sole respondent stated that he did not have any personal experience in using any respiratory support strategy. When asked if he knows someone who had used HFNC, he stated that his relative has undergone a respiratory support which he cannot specify but this intervention resulted in a favorable outcome. Further, the representative stated that tolerability is a determining factor when choosing a non-invasive respiratory support strategy, however, the respondent did not elucidate his context of tolerability. When presented with a theoretical scenario wherein a non-invasive respiratory support strategy (e.g., HFNC) has no established benefits yet, he expressed that he is willing to pay an additional Php 100 per day for this intervention.

5.3.2 Small group discussion

The small group discussion was divided into four sections focusing on the concepts of (a) factors considered in the choice of respiratory support, (b) perceived risks and benefits, (c) issues and concerns, and (d) support and funding concerns of patient groups with regards to non-invasive respiratory support strategies.

5.3.2.1. Background on the currently available treatment of COVID 19 patients

The section aimed to establish rapport and gauge previous knowledge of the patient group representatives on the COVID-19 and HFNC. Based on the narratives of the three informants, the members of their organization have some difficulties in accessing healthcare services since this access to such services requires testing for COVID-19. This greatly affects the finances of the patient who still has to pay for the needs of his/her actual medical condition. Patients who are undergoing expensive treatments (e.g., chemotherapy) experience an added financial burden.

Although they did not have firsthand experience of having COVID-19, difficulty in breathing is recognized by all informants as the most difficult sign/symptom of COVID-19 to manage. It is also important to note that in the discussion, anxiety of having COVID-19 was mentioned. This shows that this pandemic is taking its toll on people's mental health as well.

On the question on the respiratory support strategies, the patient group representatives were aware of the availability of non-invasive respiratory support strategies. However, they were not familiar with the specific types such as HFNC.

5.3.2.2. Preference and consideration on the use of respiratory support

The two informants have agreed that the protocol used (i.e., a step-wise approach on respiratory support strategies) in the actual hospital setting must be followed. This goes to show that their physicians' point of view influences their decision on this matter. Meanwhile, one informant expressed that his preference will depend on the severity of the disease upon admission. If the patient was admitted in the hospital with a case severe enough for a "step up" procedure such as HFNC, it will be his preferred strategy.

In a situational question wherein their preferred respiratory support strategy is not available to the hospital where they are admitted, all informants expressed their willingness to transfer to a hospital which offers their preferred procedure regardless of additional cost that may be incurred by transferring. They also expressed their willingness to undergo a non-invasive respiratory support strategy and even exceed their financial capacity (*mangutang*) to pay for such intervention even though its clinical benefits are yet to be determined given that it will prevent or prolong the escalation to intubation. The message being conveyed here is that, the informants are willing to pay an intervention such as HFNC just to forestall the use of mechanical ventilation. It is clear that the informants contemplate on the overall cost, the potential inconvenience that the procedure may cause, and the uncertainties in patient outcome specifically mortality in their decision making.

5.3.2.3. Perceived risk, benefits, and outcomes of the oxygenation support strategies

There is an expressed aversion to invasive mechanical ventilation because of a common fear of being immobilized. One informant stated that he will be more comfortable

undergoing a non-invasive respiratory support strategy. Meanwhile, cost and appropriateness of the intervention to specific patient needs play a major role if AHRF is added in the equation. Based on their responses, overall well-being, convenience of the procedure, and recovery rate are important considerations in the choice of respiratory support.

With these fears laid out, they generally stated that alleviation of such fears can be achieved by establishing trust with their physicians. They explained that trust with physician could be established through (1) information campaign (i.e., the physicians providing extensive information regarding the patient's treatment options) and (2) establishing good communication with both the patient and his/her family. Following this train of thought, to combat fear of uncertainty on making a well-informed decision regarding oxygenation support strategies, there must be a good line of communication between the patient, his/her family, and the physician. A constant social support, may it be in the form of emotional or informational support, is extremely vital in stressful times as it helps reduce fear and anxiety.

5.3.2.4. Support and funding of health technologies

This section focused on the perspective of patient group representatives with regards to how interventions like HFNC should be funded. They stated that the government should fund a non-invasive respiratory support strategy even though its clinical benefits are yet to be determined. Although not explicitly stated by the informants, it may be inferred that this is due to their previously discussed aversion to undergo MV. The government should only disinvest when there is clear evidence that it is not an effective intervention.

One informant mentioned that she is willing to shoulder half of the cost of the procedure (other half covered by the government). She recognizes that other people will also need subsidy from the government for their treatments. This response is also aligned with the results of the Alejandria et al. (2019) which showed Filipinos' willingness to forego personal financial or health gain for equitable access to healthcare (concept of *malasakit*).They all stated that they are willing to pay for non-invasive respiratory support strategies in case PhilHealth will remove it from their benefit package. However, one informant pointed out that he/she will question the rationale for the disinvestment.

They did not identify any legal issues, religious reasons or cultural beliefs that may hinder a patient from getting non-invasive respiratory support strategy. However, one informant raised a concern with regards to the applicability of non-invasive respiratory support strategy in patients on tracheostomy after undergoing laryngectomy procedure. Note that in a communication with Dr. Minerva Calimag of the HTAC Subcommittee on Medical and Surgical Procedures, HFNC can still be applied to the tracheostomy opening in tracheostomized patients.

Overall, the results of the Google Forms survey and SGD showed that patient group representatives are willing to undergo a non-invasive respiratory support strategy such as HFNC given that it will prevent/prolong escalation to intubation.

6. LIMITATIONS

This review recognizes the following limitations. First, as this is a rapid review, certain steps in a systematic review were abbreviated such as searching through other search databases. Second, the reviewers cite the absence of a tool to critically appraise rapid reviews. This leads to the recommendation to set a standardized tool in evaluating such studies. Hence, we cannot disregard the likelihood of possible biases which may affect the validity of the reported results. Third, most of the evidence included in this review were from the non-COVID-19 population (i.e., indirect evidence); hence, caution must be applied on the applicability of the results of the review for COVID-19 population. Fourth, the ethical and social implications assessment was not able to capture actual experiences from patients or their family members who received respiratory support as this would require the lengthy process of ethics review. Inputs were drawn from patient perception and preferences based on hypothetical situations.

Lastly, as research on the different facets of COVID-19 is on-going and rapidly evolving, the evidence presented here can rapidly change as well. Hence, updating of evidence would be necessary.

7. CONCLUSION

CLINICAL PERFORMANCE

Clinical Effectiveness:

Among COVID-19 patients, is HFNC oxygen therapy more effective than noninvasive ventilation in treating acute hypoxemic respiratory failure based on the following outcomes?

Based on the Review of Reviews

For COVID-19 population: Currently, there is insufficient evidence to show the conclusive advantage of high flow nasal cannula (HFNC) for the treatment of Acute Hypoxemic Respiratory Failure (AHRF) among COVID-19 patients when compared to other NIVs. Ongoing and future trials are anticipated to provide stronger and more conclusive evidence on the relative treatment effect of using HFNC to treat COVID-19 patients with AHRF. These trials are expected to be completed by 2021.

For non-COVID-19 population: HFNC demonstrated lower risk of mortality based on one SR involving immunocompromised patients. In terms of rate of intubation, there were conflicting evidence on the ability of HFNC to lower the rate of intubation when compared to other NIVs based on two systematic reviews. There were no included reviews that reported on outcomes length of hospital stay and length of ICU stay comparing HFNC and other NIVs.

All included systematic reviews were assessed to be critically low based on our risk of bias assessment.

Based on the Review of Local Studies

For COVID-19 population: Currently, we did not find any local studies demonstrating the relative treatment effects of HFNC versus other NIVs based on the four clinical effectiveness outcomes assessed in this review. Studies from the Lung Center of the Philippines, Philippine General Hospital, St. Luke's Medical Center, and Philippine Heart Center are ongoing and are expected to be released in December 2020 or early 2021.

For non-COVID-19 population: There is one RCT from the Philippine Heart Center demonstrating the relative treatment effects of HFNC versus NPPV (i.e., classified as NIV in this review). In all three outcomes assessed (i.e., ICU mortality, rate of intubation, length of hospital stay), HFNC did not demonstrate superior advantage over NPPV. Based on our critical appraisal, the RCT was assessed to be of high risk of bias.

Based on the Expert Opinion

Majority of the local experts consulted in this review are currently using HFNC specifically for COVID-19 patients with hypoxemic respiratory failure that do not need immediate intubation. Most of the experts also observed that patients were more comfortable in using HFNC versus mechanical ventilation.

In terms of the risk of aerosolization, the panel had slightly varied opinions on the risk of transmission brought by HFNC and if it requires a negative pressure room. One expert stated that HFNC does not pose the risk of aerosolization at all. While, two experts stated that HFNC manifests this risk but is relatively lower as compared to other NIVs such as CPAP and BiPAP. Thus, other NIVs, as they emphasized, should not be used in COVID-19 patients due to higher risk of aerosolization of respiratory droplets. Three experts, on the other hand, noted that HFNC poses the risk of aerosolization, thus, they recommended it be done with a negative pressure HVAC (heating, ventilation, and air conditioning) system or a single room if the said technology is unavailable.

Clinical Safety (aerosol generation associated with HFNC):

Among COVID-19 patients, is HFNC oxygen therapy safer than other NIVs in treating acute hypoxemic respiratory failure based on aerosolization of respiratory droplets?

For COVID-19 population: Currently, we did not find any reviews demonstrating the safety of HFNC versus other NIVs based on aerosolization of respiratory droplets.

For non-COVID-19 population: There is insufficient evidence to establish the clinical safety (in terms of aerosol generation) of HFNC when compared to other NIVs, although one study noted that increasing the pressure (CPAP) or flow rate (HFNC) would result to father distances traveled by the respiratory droplets.

Clinical guidelines, and HTA findings and recommendations on the use of HFNC:

Which country/countries have implemented HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?

Of the 15 countries/organizations reviewed for treatment guidelines on the use of HFNC, 11 (WHO, the Philippines, Australia, Canada, China, Indonesia, Japan, Malaysia, UK,US, and Vietnam) have mentioned the use of HFNC in their guidelines; three (Singapore, South Korea, European CDC) did not mention HFNC in their guidelines, and one (Thailand) was not accessible.

In terms of the nature of recommendations on the use of HFNC, four guidelines (China, the Philippines, US, and Vietnam) have provided positive recommendations but with conditions for use (i.e., use HFNC for a short trial, and if the patient condition does not improve during the trial, then intubation should not be delayed); one guideline (UK) have provided negative recommendations; and, six guidelines (WHO, Canada, Indonesia, Japan, Australia, Malaysia) have provided positive or negative recommendations, depending on the conditions for use.

What is the current position/ recommendation of HTA agencies regarding the use of HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?

None of the 13 HTA agencies reviewed has completed an assessment on the use of HFNC for COVID-19 patients with AHRF.

RESOURCE REQUIREMENTS AND ASSOCIATED COSTS

What are the resource requirements and associated costs on the use of HFNC or other NIVs in treating COVID-19 patients with acute hypoxemic respiratory failure?

The use of HFNC and other NIVs will require trained personnel, the machine and its accessories, and sufficient oxygen supply. Precautionary measures such as isolation rooms, complete PPEs, and disinfection procedures are also necessary to address the possible risk of infection transmission. In terms of the costs associated with the use of the three procedures, while there is available data on

the initial set-up cost and daily costs for HFNC and other NIVs, direct comparison of costs is not feasible because of the lacking data on the average duration of usage of both treatment modalities.

ETHICAL AND SOCIAL IMPACT ASSESSMENT

What are the ethical and social issues on the use of HFNC among COVID-19 patients with acute hypoxemic respiratory failure?

Based on the results from the Google Forms survey and small group discussion with patient group representatives, they are willing to undergo a non-invasive respiratory support strategy such as HFNC even though its clinical benefits are yet to be determined given that it will prevent/prolong escalation to intubation. They are willing to pay out-of-pocket but deems it necessary for PhilHealth to cover such technology unless there is clear evidence that it is not an effective intervention.

It is notable that one informant expressed that in terms of coverage, she is willing to opt for co-payment in consideration of other patients who also need to be covered by the government. This is consistent with the concept of *malasakit* that was strongly captured in the Social Value Principles of Filipinos affecting coverage decisions in the Philippines by Alejandria et al., 2019.

8. DECLARATION OF CONFLICT OF INTERESTS

The reviewers declare no conflict of interests.

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10.APPENDICES

Appendix 1. Questionnaire on Expert Opinion on the Use of HFNC (Clinical Experience)

Appendix 2. Questionnaire on Expert Opinion on the Use of HFNC (Resource Requirements and Associated Costs)

Appendix 3a. Questionnaire on Ethical and Social Impact Assessment (Google Forms)

Appendix 3b. Questionnaire on Ethical and Social Impact Assessment (SGD)

Appendix 4. Characteristics of Excluded Studies After Full-text Review

Appendix 5. Critical Appraisal of Included Reviews

Appendix 6. COVID-19 Treatment Guidelines of Organizations or Countries on the Use of HFNC

Appendix 1. Questionnaire on Expert Opinion on the Use of HFNC (Clinical Experience)

Data Extraction Form

Expert opinion

in the proposed health technology

High Flow Nasal Cannula (HFNC) for COVID-19 patients with Acute Hypoxemic Respiratory Failure

Details of the respondent:

Name of Expert:
Affiliation/Institution:

I confirm that my responses in this form represent the stand of the institution and/or organization I am currently affiliated with. I understand and agree that **all disclosed information in this submission may be included in the published report**, in accordance with the existing laws and policies of the country. Further, I understand that any false or misleading information provided in this submission may lead to appropriate legal actions by the Department of Health.

CONFORME:

_____
Signature over Printed Name

Technical Expertise/ Clinician Questions

In the current COVID-19 pathway, when is HFNC used?

Some points to consider:

- *Population whom HFNC is used (e.g., patients with AHRF)*
- *Criteria on qualifying a patient to receive HFNC*
- *Treatment guideline followed*

Answer:

What is the appropriate comparator for HFNC? (Our draft rapid review currently compares HFNC with conventional oxygen therapy and other non-invasive ventilation such as CPAP, BiPAP)

Answer:

Clinical experience on the use of HFNC

What is your experience on the use of HFNC for COVID-19 patients with acute hypoxemic respiratory failure (AHRF)?

Points to consider:
In line with the research questions of the rapid review, the DOH-HTA Unit prefers information comparing HFNC in terms of a) observable change in mortality rates; b) observable change in escalation to intubation; c) observable change in hospital length of stay; d) observable change in ICU length of stay for the following comparators:

- *Versus Conventional Oxygen Therapy (COT)*

Answer:

- *Versus Other Non-Invasive Ventilation (e.g., CPAP, BiPAP)*

Answer:

Are there other clinically meaningful outcomes which should be considered in assessing HFNC? If yes, kindly specify and define these outcomes.

Answer:

Is there a preference to use HFNC over other non-invasive therapies (e.g., COT, other NIVs) or invasive/mechanical ventilation? Kindly justify.

Answer:

Availability of studies

Are you aware of a local study (published or unpublished, observational or RCT) that demonstrated the relative treatment effects of HFNC compared to COT or other NIVs for COVID-19 patients with AHRF? (*If yes, please provide details (if ongoing) or full-text copy of the said study as attachment.)*

Are you aware of any other sources of data that assessed the clinical performance of HFNC versus COT or other NIVs for COVID-19 patients with AHRF? (*If yes, please provide the details (if ongoing) or full-text copy as attachment.)*

Answer:

Are you aware of any local studies or any other data sources (published or unpublished, observational or RCT) that demonstrated differences in treatment outcomes and mortality rates in the use of HFNC compared to invasive/ mechanical ventilation in COVID-19 patients with AHRF (*If yes, please provide the details (if ongoing) or full-text copy as attachment.)*

Answer:

Other information

Is there any information that you would like the DOH-HTA Unit to consider in the assessment of HFNC for COVID-19 patients with AHRF? If yes, kindly provide them below.

Answer:

Appendix 2. Questionnaire on Expert Opinion on the Use of HFNC (Resource Requirements and Associated Costs)

Data Extraction Form

Resource Requirements

in the proposed health technology

High Flow Nasal Cannula (HFNC) for COVID-19 patients with Acute Hypoxemic Respiratory Failure

Details of the respondent:

Name of Expert:
Affiliation/Institution:

I confirm that my responses in this form represent the stand of the institution and/or organization I am currently affiliated with. I understand and agree that **all disclosed information in this submission may be included in the published report**, in accordance with the existing laws and policies of the country. Further, I understand that any false or misleading information provided in this submission may lead to appropriate legal actions by the Department of Health.

CONFORME:

_____
Signature over Printed Name

All questions pertain to the use of health technologies (i.e., HFNC, COT, other NIVs, invasive/mechanical ventilation) for COVID-19 patients with acute hypoxemic respiratory failure.

Technical Expert/ Clinician Questions

Adverse Events

- Does the use of the following health technologies cause any foreseeable side effects and/or adverse effects (AEs)? What are these side effects and/or AEs? Do they require preventive management, monitoring or additional treatment cost?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Human Resource Needs

- Are there personnel requirements (e.g., respiratory therapist, pulmonologist, nurses) **during hook-up, machine set-up, monitoring, and during discontinuation of the following health technologies? If yes, kindly elaborate.**

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Training of personnel

- Is a special training necessary before a personnel can administer the following health technologies to a patient with acute hypoxemic respiratory failure? *(Kindly elaborate further if there is special training necessary)*

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Consumables

- What are the items to be used before, during, and after the use of the following health technologies? Examples of which are sterile pack, sterile gowns, disposable corrugated tubings, nasal cannula, etc.

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Preparation of the patient

- Are there necessary preparations (e.g., administration of a drug) that should be done or administered prior to initiation of the following health technologies to a patient with acute hypoxemic respiratory failure? If yes, what are these preparations and what are their roles in these health technologies?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or

			mechanical ventilation):

Administrative concerns

- Does your hospital currently have the necessary medical equipment for the following health technologies for patient management? How many? Are all of them operational? Do you know other hospitals which are currently using these health technologies for COVID-19?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Infrastructure

- Are there specialized rooms needed for the use of the following health technologies? Is it done in the single wards? If used in a shared ward, is the room limited to cohorts of confirmed patients diagnosed with COVID-19 only?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- Are there special equipment (e.g., ultrasound machine) needed apart from the machine for the following health technologies? If so, please identify these equipment and their role in the use of such health technologies.

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Projected initial and daily costs

- How much is the projected initial and daily cost of using the machine for the following health technologies? For how long do patients use the machine?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- What are the cost items (and corresponding cost values) considered in the daily cost of using a machine for the following health technologies? Does this already include the consumables (and all other associated costs), or the cost only reflects the usage of the machine?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- Among the resources identified, what are the cost drivers (and corresponding cost values) considered in the daily use of a machine in the use of the following health technologies? How do these identified cost drivers affect the daily cost of these health technologies (e.g., causes an increase in the daily cost)?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Health Systems Impact

- Are there organizational changes and additional costs likely needed in the local health system or health settings required in adopting the health technology?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- Is training of health facility end users needed to use the health technology?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- How would these numbers change if the health technology was used for COVID (e.g. separate wards, additional PPE, additional training etc.)?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

- How many hospitals would be able to accommodate converting the health technology from non-COVID to COVID use? If possible, indicate the timeline on how much time needed for each of the facilities to be converted.

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Other resource needs

- Are there other implementation concerns not covered by the earlier questions?

Answer (for HFNC):	Answer (for COT):	Answer (for other NIVs):	Answer (for invasive or mechanical ventilation):

Appendix 3a. Questionnaire on Ethical and Social Impact Assessment (Google Forms)

Questionnaire on the Ethical and Social Implications of Using High Flow Nasal Cannula (HFNC)
Mga katanungan ukol sa Etikal at Panlipunang Implikasyon ng Paggamit ng High Flow Nasal Cannula (HFNC)

Context and Background

In early 2020, the World Health Organization (WHO) declared novel coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 160 countries and regions. In the Philippines, there have been over 396,395 COVID-19 cases with 7,539 deaths as of 8 November 2020 (Department of Health, 2020). To date, there is no known treatment for COVID-19 (Dong, Du & Gardner, 2020).

Sa simula ng taong 2020, nagdeklara ang World Health Organization (WHO) ng pandemya dahil sa pagkalat sa buong mundo ng novel coronavirus disease 2019 o mas kilala sa tawag na COVID-19. Sa Pilipinas, tinatayang mayroong 396,395 kaso ng COVID-19 at 7,539 na patay ayon sa datos ng Department of Health noong Nobyembre 8, 2020. (Department of Health, 2020). Hanggang ngayon, wala pa ring natutukoy na lunas para sa sakit na ito. (Dong, Du & Gardner, 2020).

The symptoms of COVID-19 can be mild, moderate or severe. Difference in the signs and symptoms of mild, moderate, and severe COVID-19 infections are shown in *Figure 1*. Mild cases of COVID-19 usually experiences coughing, fever, and tiredness. In addition to these symptoms, moderate cases suffer from difficulty breathing and mild pneumonia. Meanwhile, severe COVID-19 cases may suffer from severe pneumonia and organ failure. These conditions may lead to a complication called acute hypoxemic respiratory failure (AHRF). AHRF prevents enough oxygen from getting to the lungs and the blood (Anesi, 2020). A patient with AHRF may experience shortness of breath, restlessness, anxiety, higher than average respiratory and heart rate, excessive sweating, and bluish discoloration of the skin.

Ang mga taong may COVID-19 ay maaring makaranas ng iba't ibang sintomas depende sa kung gaano kalubha ang impeksyon sa kanilang katawan. Ipinapakita sa Larawan 1 ang iba't ibang sintomas na ito. Sa mga mild na kaso, maaring makaranas ng ubo, lagnat at pagod. Dagdag pa sa mga sintomas na ito, ang mga pasyente naman na may moderate na kaso ng COVID-19 ay maaari ring makaranas ng hirap sa paghinga at magkaroon ng pulmonya. Samantala, ang severe o pinaka-malalang kaso ng COVID-19 ay maaaring magdulot ng mas malalang kaso ng pulmonya at organ failure sa mga pasyente. Dahil dito, ang mga pasyenteng may COVID-19 ay maaaring makaranas ng komplikasyon na tinatawag na Acute Hypoxemic Respiratory Failure o AHRF. Ang AHRF ay kondisyon kung saan hindi nakakatanggap ng sapat na oxygen ang baga at ang buong katawan (Anesi, 2020). Ang pasyente na may AHRF ay maaaring makaranas ng pagkahingal, pagkabalisa, mabilis na paghinga, mabilis pagtibok ng puso, ,sobrang pagpapawis, at pagiging asul ng balat.

Figure 1. Difference in signs and symptoms between mild, moderate, and severe cases of COVID-19 according to the World Health Organization

Larawan 1. Iba't ibang sintomas ng COVID-19 depende sa lubha ng impeksyon

There are two respiratory support strategies to help COVID-19 patients with AHRF in their breathing, namely *invasive* or *non-invasive*. *Invasive respiratory support* delivers air directly to the lungs by inserting a tube through the mouth or the nose. An example would be mechanical ventilation or intubation (*Filipino translation, Pagtubo*). Meanwhile, *non-invasive respiratory support strategies* deliver air through a sealed mask, nasal prongs or cannula placed over the mouth, the nose, or the whole face (Luo et al., 2017). Examples of these non-invasive respiratory support strategies are conventional oxygen therapy (COT), High Flow Nasal Cannula (HFNC), Bi-level Positive Airway Pressure (BiPAP), and Continuous Positive Airway Pressure (CPAP). For better understanding of their difference, illustrations are provided in *Figure 2 a-c*.

May iba't ibang paraan upang matulungan sa paghinga ang mga pasyenteng may COVID-19 na nakakaranas ng AHRF. Ito ay tinatawag na respiratory support. Ang respiratory support ay maaaring invasive o non-invasive. Ang invasive respiratory support ay gumagamit ng isang tubo na ipinapasok sa ilong o sa bibig ng pasyente upang direktang magbigay ng hangin sa baga. Halimbawa nito ay mechanical ventilation o intubation, o maaaring pamilyar sa atin sa tawag na 'pagtutubo'. Samantala, ang mga non-invasive respiratory support naman ay nagsusuplay ng hangin sa pasyente gamit ang face mask, o prongs o cannula na nilalagay sa ilong (Luo et al.,

2017). Ang mga halimbawa ng non-invasive respiratory support ay ang conventional oxygen therapy (COT), High Flow Nasal Cannula (HFNC), Bi-level Positive Airway Pressure (BiPAP), at Continuous Positive Airway Pressure (CPAP). Upang mas madaling maintindihan ang pagkakaiba-iba ng mga ito, maaaring tingnan ang mga larawan sa Larawan 2a-c.

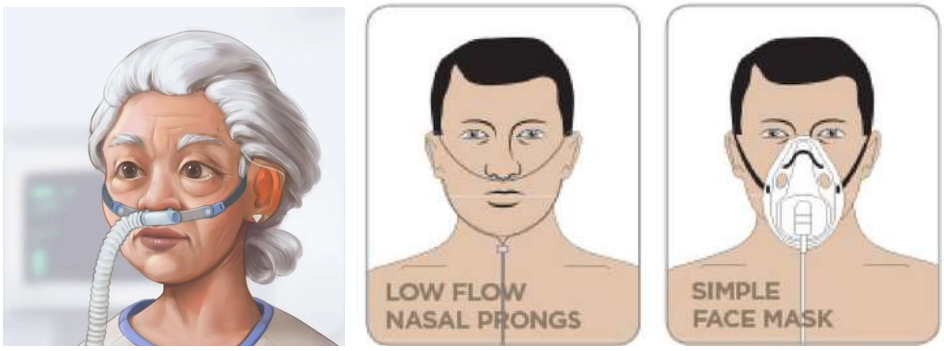

Figure 2a. Illustration of Patients receiving Conventional Oxygen Therapy (COT) using nasal prongs.

Note: COT (may also be called LFNC) and HFNC both use nasal cannula. The difference between COT (or LFNC) and HFNC is that HFNC provides a higher flow rate which is up to 60 liters per minute (hence, it is called High Flow NC). Meanwhile, COT can provide 1-6 liters of oxygen per minute (hence, it is called Low Flow NC).

Larawan 2a. Larawan ng mga Pasyente na Binibigyan ng Conventional Oxygen Therapy (COT) gamit ang nasal prongs, cannula, at face mask

Tandaan: Parehong gumagamit ng nasal cannula ang COT (o maari ring tawaging LFNC) at ang HFNC. Ang pinagkaiba lamang ng COT (o LFNC) at ng HFNC ay nagbibigay ng mas mataas na bilis ng daloy ng oxygen ang HFNC na umaabot ng 60 litro kada minuto (kaya ito tinawag na high flow NC), habang ang COT ay nagbibigay lamang ng 1 -6 litro ng oxygen kada minuto (kaya ito tinawag na low flow NC).

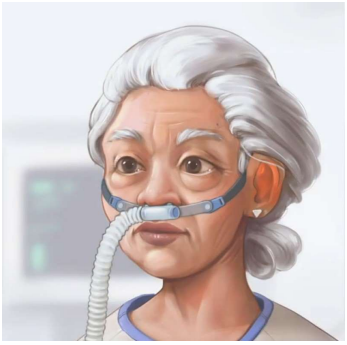

Figure 2b. Illustration of a Patient receiving High Flow Nasal Cannula (HFNC)

Note: COT (may also be called LFNC) and HFNC both use nasal cannula. The difference between COT (or LFNC) and HFNC is that HFNC provides a higher flow rate which is up to 60 liters per minute (hence, it is called High Flow NC). Meanwhile, COT can provide 1-6 liters of oxygen per minute (hence, it is called Low Flow NC).

Larawan 2b. Larawan ng Pasyente na Binibigyan ng oxygen gamit ang High Flow Nasal Cannula (HFNC)

Tandaan: Parehong gumagamit ng nasal cannula ang COT (o maari ring tawaging LFNC) at ang HFNC. Ang pinagkaiba lamang ng COT (o LFNC) at ng HFNC ay nagbibigay ng mas mataas na bilis ng daloy ng oxygen ang HFNC na umaabot ng 60 litro kada minuto (kaya ito tinawag na high flow NC), habang ang COT ay nagbibigay lamang ng 1 -6 litro ng oxygen kada minuto (kaya ito tinawag na low flow NC).

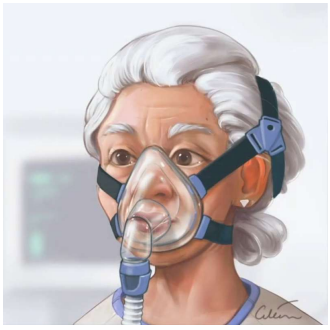

Figure 2c. Illustration of a Patient receiving either Bi-Level Positive Airway Pressure (BiPAP) or Continuous Positive Airway Pressure (CPAP)

Larawan 2c. Larawan ng Pasyente na Binibigyan ng oxygen gamit ang Bi-Level Positive Airway Pressure (BiPAP) o Continuous Positive Airway Pressure (CPAP)

The Health Professionals Alliance Against COVID-19 (HPAAC), an alliance of different medical societies, came up with a way to determine when to use non-invasive or invasive respiratory support for COVID-19 patients. This is shown in *Figure 3*.

Ang Health Professionals Alliance Against COVID-19 (HPAAC), isang samahan ng mga grupong medikal, ay gumawa ng guidelines upang matukoy kung kailan kailangang gumamit ng non-invasive o invasive respiratory support sa mga pasyente ng COVID-19 na nahihirapan sa paghinga. Makikita ito sa Larawan 3.

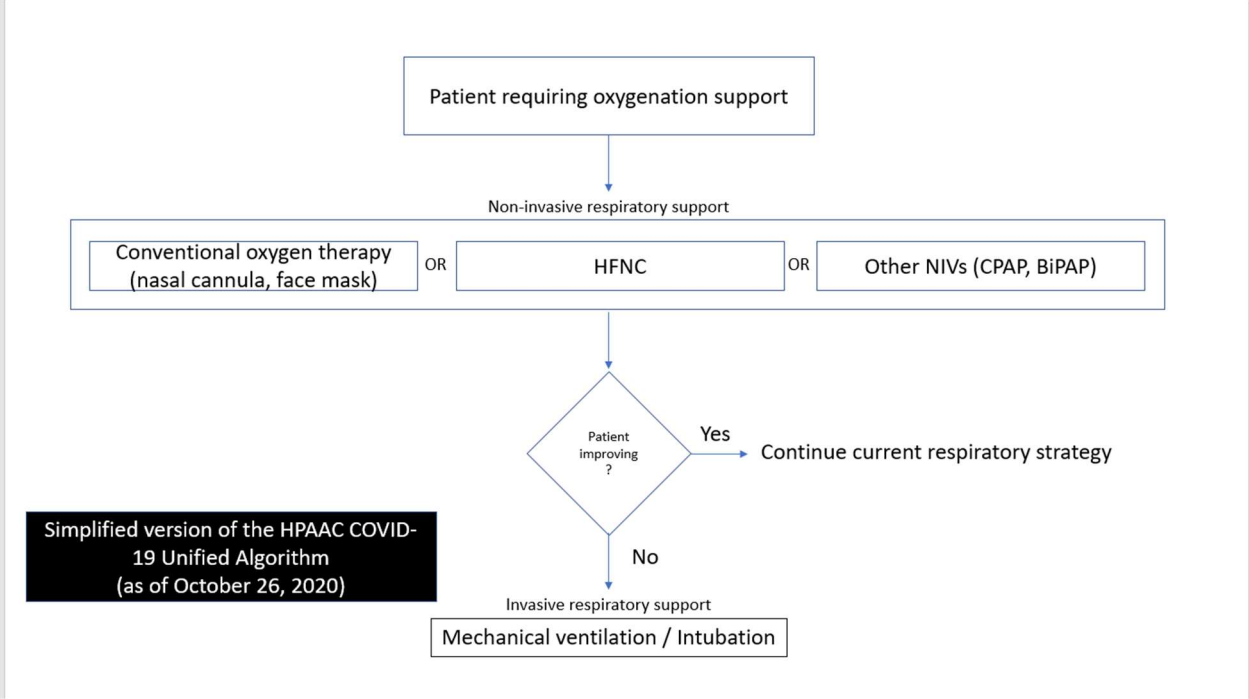

Figure 3. *HPAAC Unified Algorithm for the Management of Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Patients*

Larawan 3. Pamamaraan ng HPAAC sa Paggamot ng mga Pasyente ng COVID-19 na may AHRF

However, upon consultation with experts, it was found out that the HPAAC guidelines is not used in the actual practice. Experts from various medical societies, and private and public hospital detailed a different treatment pathway for COVID-19 patients with AHRF which uses a stepwise approach in determining which respiratory support strategy to use. This is showed in *Figure 4*.

Ngunit, ayon sa karanasan ng mga eksperto, iba ang ginagamit na paraan sa mga ospital sa pagtukoy kung ano ang nararapat na respiratory support strategy na gagamitin sa pasyente. Sila ay gumagamit ng stepwise na pamamaraan para dito. Ito ay pinapakita sa Larawan 4.

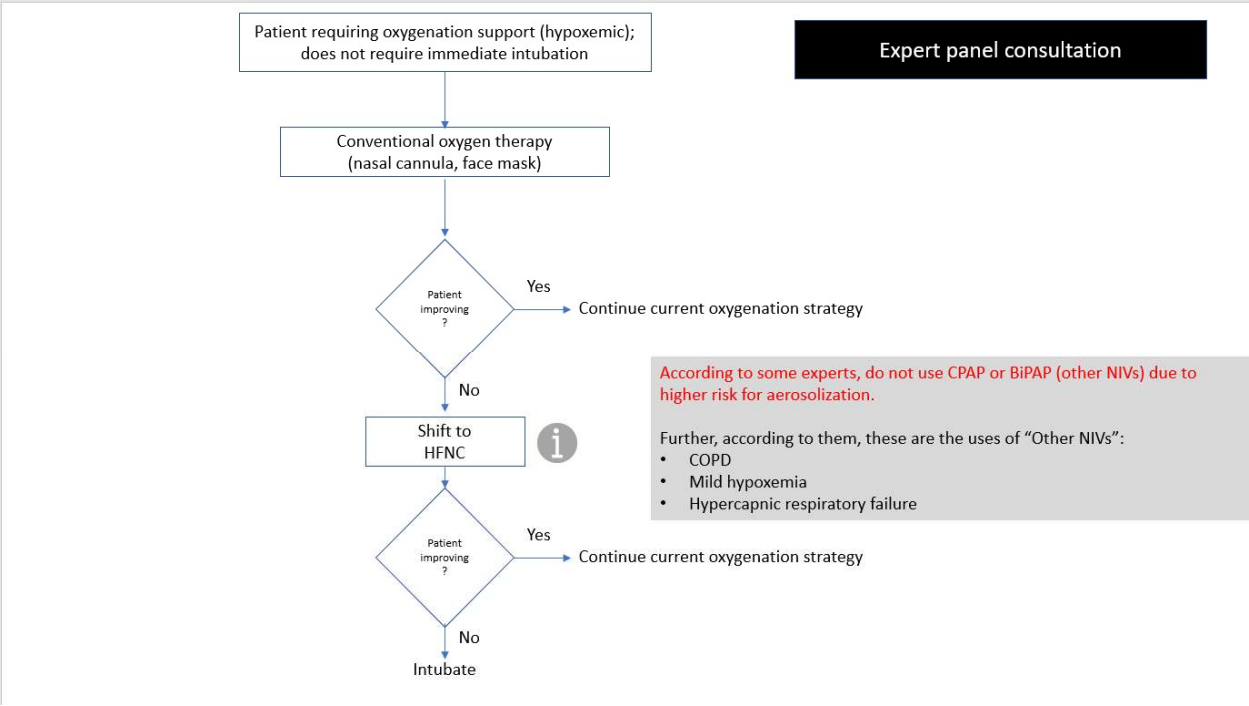

Figure 4. Algorithm used in the actual hospital setting for treatment of COVID-19 patients with Acute Hypoxemic Respiratory Failure.

Larawan 4. Pamamaraan ng mga ospital sa pagtukoy ng tamang respiratory support strategy para sa mga pasyente ng COVID-19 na may Acute Hypoxemic Respiratory Failure.

Currently, PhilHealth covers additional medical services needed by COVID-19 patients with critical pneumonia. Additionally, the Department of Health recently funded the purchase of 200 units of HFNC among other medical equipment which will be useful in addressing the needs of COVID-19 patients.

Sa kasalukuyan, kasama sa PhilHealth benefit package ang mga karagdagang serbisyong medikal na kailangan ng mga pasyenteng may malubhang pulmonya dahil sa COVID-19. Naglaan rin ng pera ang Kagawaran ng Kalusugan para sa pagbili ng 200 na yunit ng HFNC kabilang ang iba pang kagamitang pangmedikal na kakailanganin para sa gamutan ng mga pasyenteng may COVID-19.

Currently, there is not enough published evidence to show that HFNC is effective compared to other non-invasive respiratory support strategies in addressing AHRF in COVID-19 patients in terms of decreasing mortality, length of ICU stay, length of hospital stay, and preventing patient from advancing to invasive respiratory support. Since evidence on COVID-19 is rapidly evolving, clarity on the effectiveness of HFNC may be expected when ongoing local and international studies are completed.

Sa kasalukuyan, wala pang sapat na ebidensyang nagpapakita na ang HFNC para sa mga pasyente ng COVID-19 na may AHRF ay may mabisang epekto kumpara sa iba pang non-invasive respiratoty support strategy base sa dami ng pagkamatay, tagal ng pananatili sa ICU, tagal ng pananatili sa ospital, at pag-iwas na mailagay ang pasyente sa invasive respiratory support. Dahil ang ebidensya sa COVID-19 ay mabilis na lumalabas at nadaragdagan, maaari tayong makakuha

ng mas malinaw na konteksto sa pagkabisa ng HFNC kapag nakumpleto ang mga lokal at internasyonal na pag-aaral na kasalukuyang isinasagawa.

The focused group discussion will zoom in on patient groups' perception and preferences when it comes to the use of *non-invasive respiratory support strategies* for COVID-19 patients with AHRF. To help in the discussion, illustrations and details of the non-invasive procedures are shown in *Table 1*.

Ang talakayang ito ay naglalayong mas alamin pa ang mga persepsyon/pang-unawa at kagustuhan ng mga grupo ng pasyente sa usapin ng paggamit ng iba't-ibang non-invasive respiratory support sa paglunas ng AHRF sa mga taong may COVID-19. Bilang gabay sa talakayang ito, ang mga detalye ukol sa iba't-ibang non-invasive respiratory support ay makikita. sa Table 1.

Table 1. Characteristics of the different non-invasive respiratory support strategies

	Non-invasive oxygenation support strategies			
	Conventional Oxygen Therapy (COT)	**High Flow Nasal Cannula (HFNC)**	**Bi-Level Positive Airway Pressure (BiPAP)**	**Continuous Positive Airway Pressure (CPAP)**
Description	The first line of treatment when not enough oxygen is delivered to the lungs. COT delivers **1-6 liters of oxygen per minute** through face masks, nasal prongs, or cannulas. This is also called Low Flow Nasal Cannula (LFNC). Note that LFNC and HFNC both use nasal cannula to deliver oxygen. However, they differ in flow rates as HFNC provides a higher flow rate compared to LFNC.	Can be used in patients when not enough oxygen is being delivered to their lungs. This procedure delivers 100% **humidified and heated oxygen** at **up to 60 liters per minute**. Note that LFNC and HFNC both use nasal cannula to deliver oxygen. However, they differ in flow rates as HFNC provides a higher flow rate compared to LFNC.	Can be used in patients when not enough oxygen is being delivered to their lungs. . **Delivers pressurized air using two pressure settings**, one for inhaling and one for exhaling	Can be used in patients when not enough oxygen is being delivered to their lungs. Delivers constant **pressurized air** using a **single pressure setting throughout.**
Advantage	• Simple and well tolerated by patients	• Decreases swelling of the airways • Improves clearance of secretions • Delivers more oxygen compared to COT	• Ideal for patients with other lung conditions such as Chronic Obstructive Pulmonary Disease (COPD)	• Prevents collapsed lung (atelectasis)

Disadvantages	• Oxygen delivery is dependent on the patient's work of breathing • Not appropriate for patients who cannot breathe on their own	• Poses risk for generation of droplets that may lead to transmission of the virus.	• Not for patients who cannot breathe on their own • Not comfortable to the patient. • Not for patients with fear of tight or crowded spaces • Increased risk for generation of droplets that may lead to transmission of the virus compared to HFNC	• Not for patients who cannot breathe on their own • Not comfortable to the patient. • Not for patients with fear of tight or crowded spaces • Increased risk for generation of droplets that may lead to transmission of the virus compared to HFNC
Estimated initial cost (Set-up cost)	Pending data	Php 8,144.00 - 10,000.00	Php 14,549.25	Php 14,549.25
Estimated cost per day	Pending data	Php 1,100.00 – 2,030.00	Php 1,840.00 - 2,860.00	Php 1,840.00 - 2,860.00

Table 1. Mga katangian ng iba't ibang non-invasive respiratory support strategies

	Non-invasive oxygenation support strategies			
	Conventional Oxygen Therapy (COT)	***High Flow Nasal Cannula (HFNC)***	***Bi-Level Positive Airway Pressure (BiPAP)***	***Continuous Positive Airway Pressure (CPAP)***

Deskripsyon	*Paunang binibigay sa pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Nakapagbibigay ng **1-6 na litro ng oxygen kada minuto** gamit ang face mask o nasal prongs o cannula.* *Ito ay tinatawag ring Low Flow Nasal Cannula (LFNC) kung ang ginamit para sa COT ay nasal cannula. Tandaan na ang LFNC at HFNC ay parehas gumagamit ng nasal cannula upang ideliver ang oxygen ngunit nagkaiba sila sa bilis ng daloy ng oxygen bilang mas mabilis ang daloy sa HFNC kumpara sa LFNC.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Nakakapagbigay ng hanggang **60 litro ng oxygen kada minuto.** Ang oxygen na naibibigay ng HFNC ay humidified para hindi makapagdulot ng panunuyo ng daluyan ng hangin. Ang oxygen na dala ng HFNC ay kapareho sa temperatura ng ating katawan.* *Tandaan na ang LFNC at HFNC ay parehas gumagamit ng nasal cannula upang ideliver ang oxygen ngunit nagkaiba sila sa bilis ng daloy ng oxygen bilang mas mabilis ang daloy sa HFNC kumpara sa LFNC.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Ito ay nagbibigay sa pasyente ng **hangin gamit ang dalawang magkaibang lakas ng pressure**, isa para sa pag-inhale at isa para sa pag-exhale.* *.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Ito ay nagbibigay sa pasyente ng **hangin** gamit ang **iisang lakas ng pressure** na tuloy-tuloy na binibigay.*
Benepisyo	• *Simple at hindi mahirap para sa pasyente*	• *Binabawasan ang pamamaga ng daluyan ng hangin ng pasyente* • *Pinapadali ang pagtanggal ng mga plema o iba pang nakabara sa daluyan ng hangin ng pasyente*	• *Mainam para sa mga pasyente ng COVID-19 at may AHRF na may iba pang kondisyon sa baga tulad ng Chronic Obstructive Pulmonary Disease (COPD)*	• *Naiiwasan ang atelectasis o ang pag-collapse ng baga*

		• *Mas maraming naibibigay na oxygen kumpara sa COT*		
Kakulangan	• *Nakadepende ang epekto nito sa kapasidad ng pasyente na mag-inhale at exhale.* • *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta).*	• *Maaring magresulta sa droplets na maaring magsanhi ng pagkalat ng virus.*	• *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta)* • *Hindi kumportable para sa pasyente* • *Hindi maaaring gamitin sa pasyenteng may takot sa masisikip o matataong espasyo.* • *Mas mataas na posibilidad na magresulta sa droplets na maaring magsanhi ng pagkalat ng virus kumpara sa HFNC.*	• *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta)* • *Hindi kumportable para sa pasyente* • *Hindi maaaring gamitin sa pasyenteng may takot sa masisikip o matataong espasyo.* • *Mas mataas na posibilidad na magresulta sa droplets na maaring magsanhi ng pagkalat ng virus kumpara sa HFNC.*
Paunang gastos para sa pag set-up ng makina	*Wala pang datos*	*Php 8,144.00 - 10,000.00*	*Php 14,549.25*	*Php 14,549.25*
Arawang gastos	*Wala pang datos*	*Php 1,100.00 – 2,030.00*	*Php 1,840.00 - 2,860.00*	*Php 1,840.00 - 2,860.00*

Questions [Google Forms]

Given the information provided above, please answer the following questions. Note that there is no correct or wrong answer to these questions. Do not hesitate to ask questions and clarify points that are unclear to you.

Sa mga naibigay/naipresenta/nailahad na impormasyon, mangyari po lamang na sagutin ang mga sumusunod na tanong. Tandaan na walang tama o maling sagot sa mga katanungang ito. Huwag mag-atubiling magtanong at linawin ang mga puntong hindi malinaw sa iyo.

To protect and maintain your privacy, some of the questions will be given to you through Google Forms. Please be assured that your response to these questions will be handled in such a way that will preserve your anonymity. You can access the questions using the following links. **Please choose only one link between the English and Filipino version**:

Upang maprotektahan at mapanatili ang inyong pagkapribado, ang mga piling tanong ay ibibigay sa inyo sa pamamagitan ng Google Forms. Sinisiguro namin sa inyo na ang inyong mga kasagutan sa mga tanong ay pangangasiwaan nang mabuti upang mapanatili ang inyong pagka-anonimo. Maari ninyong masagutan ang mga tanong gamit ang mga sumusunod na link. ***Maari lamang na pumili ng isang link na sasagutan sa pagitan ng English at Filipino na bersyon****:*

English version: https://forms.gle/4z2QGw1CTXaesj6XA

Filipino version: https://forms.gle/vMt8pbXK26H7JjHs7

1. Based on information on the different respiratory support for COVID-19 patients with AHRF (Refer to *Table 1*), arrange the following non-invasive respiratory support strategies according to which procedure you would like to be given to you first to your least preferred procedure (COT, HFNC, BiPAP, CPAP).
    a. Probing question
        What factors did you consider in selecting your least and preferred procedure?

    Base sa mga impormasyon na ibinigay tungkol sa mga respiratory support para sa mga pasyente ng COVID-19 na may AHRF (Table 1), pagsunod-sunurin ang mga ito batay sa kung alin ang iyong pinakagustong pamamaraan (COT, HFNC, BiPAP, CPAP).
        Anu-anong mga kadahilanan ang iyong kinonsidera sa pagpili ng iyong pinakagusto at hindi gustong pamamaraan ng respiratory support?

2. How much more are you willing to pay for non-invasive respiratory support that has no clear/ established advantage yet over a conventional oxygen therapy, in terms of:
    i. patient mortality
    ii. length of ICU stay
    iii. length of hospital stay
    iv. escalation to intubation

    Gaanong halaga pa ang malugod mong babayaran para sa non-invasive respiratory support na wala pang malinaw na patunay kung ito nga ay nagbibigay ng mas malaking benepisyo sa pasyente kumpara sa conventional oxygen therapy pagdating sa:
    i. Pagkamatay ng pasyente

ii. *Haba ng pamamalagi sa ICU*
iii. *Haba ng pamamalagi sa hospital*
iv. *Pagiwas sa pagtutubo sa pasyente*

3. Have you had experience difficulty in breathing? What helped you?
    a. Probing: If it was oxygen, how did the oxygen supplementation helped you? Were there any discomforts?

Nakaranas na po ba kayo na mahirapan sa paghinga? Ano ang nakatulong sa iyo para makahinga ng maayos?

a. Probing: Kung ito ay oxygen supplementation, paano ito nakatulong sa iyong paghinga? May mga masamang pakiramdam ka bang ininda?

4. Do you know someone (relative or friend) who had used HFNC? What was the result of the treatment?

Mayroon ka bang kakilala (maaari ito ay isang kamag-anak o kaibigan) na nakagamit na ng HFNC? Ano ang naging resulta ng gamot gamutan gamit ang HFNC?

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Appendix 3b. Questionnaire on Ethical and Social Impact Assessment (online SGD)

Questionnaire on the Ethical and Social Implications of Using High Flow Nasal Cannula (HFNC)
Mga katanungan ukol sa Etikal at Panlipunang Implikasyon ng Paggamit ng High Flow Nasal Cannula (HFNC)

Context and Background

In early 2020, the World Health Organization (WHO) declared novel coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 160 countries and regions. In the Philippines, there have been over 396,395 COVID-19 cases with 7,539 deaths as of 8 November 2020 (Department of Health, 2020). To date, there is no known treatment for COVID-19 (Dong, Du & Gardner, 2020).

Sa simula ng taong 2020, nagdeklara ang World Health Organization (WHO) ng pandemya dahil sa pagkalat sa buong mundo ng novel coronavirus disease 2019 o mas kilala sa tawag na COVID-19. Sa Pilipinas, tinatayang mayroong 396,395 kaso ng COVID-19 at 7,539 na patay ayon sa datos ng Department of Health noong Nobyembre 8, 2020. (Department of Health, 2020). Hanggang ngayon, wala pa ring natutukoy na lunas para sa sakit na ito. (Dong, Du & Gardner, 2020).

The symptoms of COVID-19 can be mild, moderate or severe. Difference in the signs and symptoms of mild, moderate, and severe COVID-19 infections are shown in *Figure 1*. Mild cases of COVID-19 usually experiences coughing, fever, and tiredness. In addition to these symptoms, moderate cases suffer from difficulty breathing and mild pneumonia. Meanwhile, severe COVID-19 cases may suffer from severe pneumonia and organ failure. These conditions may lead to a complication called acute hypoxemic respiratory failure (AHRF). AHRF prevents enough oxygen from getting to the lungs and the blood (Anesi, 2020). A patient with AHRF may experience shortness of breath, restlessness, anxiety, higher than average respiratory and heart rate, excessive sweating, and bluish discoloration of the skin.

Ang mga taong may COVID-19 ay maaring makaranas ng iba't ibang sintomas depende sa kung gaano kalubha ang impeksyon sa kanilang katawan. Ipinapakita sa Larawan 1 ang iba't ibang sintomas na ito. Sa mga mild na kaso, maaring makaranas ng ubo, lagnat at pagod. Dagdag pa sa mga sintomas na ito, ang mga pasyente naman na may moderate na kaso ng COVID-19 ay maaari ring makaranas ng hirap sa paghinga at magkaroon ng pulmonya. Samantala, ang severe o pinaka-malalang kaso ng COVID-19 ay maaaring magdulot ng mas malalang kaso ng pulmonya at organ failure sa mga pasyente. Dahil dito, ang mga pasyenteng may COVID-19 ay maaaring makaranas ng komplikasyon na tinatawag na Acute Hypoxemic Respiratory Failure o AHRF. Ang AHRF ay kondisyon kung saan hindi nakakatanggap ng sapat na oxygen ang baga at ang buong katawan (Anesi, 2020). Ang pasyente na may AHRF ay maaaring makaranas ng pagkahingal, pagkabalisa, mabilis na paghinga, mabilis pagtibok ng puso, ,sobrang pagpapawis, at pagiging asul ng balat.

Figure 1. Difference in signs and symptoms between mild, moderate, and severe cases of COVID-19 according to the World Health Organization

Larawan 1. Iba't ibang sintomas ng COVID-19 depende sa lubha ng impeksyon

There are two respiratory support strategies to help COVID-19 patients with AHRF in their breathing, namely *invasive* or *non-invasive*. *Invasive respiratory support* delivers air directly to the lungs by inserting a tube through the mouth or the nose. An example would be mechanical ventilation or intubation (*Filipino translation, Pagtubo*). Meanwhile, *non-invasive respiratory support strategies* deliver air through a sealed mask, nasal prongs or cannula placed over the mouth, the nose, or the whole face (Luo et al., 2017). Examples of these non-invasive respiratory support strategies are conventional oxygen therapy (COT), High Flow Nasal Cannula (HFNC), Bi-level Positive Airway Pressure (BiPAP), and Continuous Positive Airway Pressure (CPAP). For better understanding of their difference, illustrations are provided in *Figure 2 a-c*.

May iba't ibang paraan upang matulungan sa paghinga ang mga pasyenteng may COVID-19 na nakakaranas ng AHRF. Ito ay tinatawag na respiratory support. Ang respiratory support ay maaaring invasive o non-invasive. Ang invasive respiratory support ay gumagamit ng isang tubo na ipinapasok sa ilong o sa bibig ng pasyente upang direktang magbigay ng hangin sa baga. Halimbawa nito ay mechanical ventilation o intubation, o maaaring pamilyar sa atin sa tawag na 'pagtutubo'. Samantala, ang mga non-invasive respiratory support naman ay nagsusuplay ng hangin sa pasyente gamit ang face mask, o prongs o cannula na nilalagay sa ilong (Luo et al.,

2017). Ang mga halimbawa ng non-invasive respiratory support ay ang conventional oxygen therapy (COT), High Flow Nasal Cannula (HFNC), Bi-level Positive Airway Pressure (BiPAP), at Continuous Positive Airway Pressure (CPAP). Upang mas madaling maintindihan ang pagkakaiba-iba ng mga ito, maaaring tingnan ang mga larawan sa Larawan 2a-c.

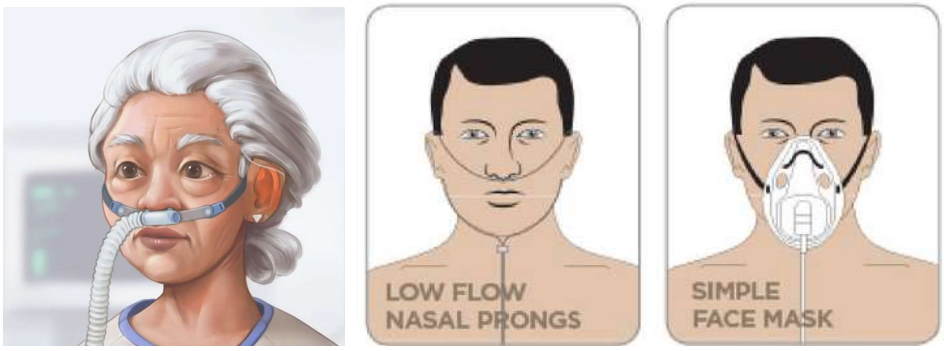

Figure 2a. Illustration of Patients receiving Conventional Oxygen Therapy (COT) using nasal prongs.

Note: COT (may also be called LFNC) and HFNC both use nasal cannula. The difference between COT (or LFNC) and HFNC is that HFNC provides a higher flow rate which is up to 60 liters per minute (hence, it is called High Flow NC). Meanwhile, COT can provide 1-6 liters of oxygen per minute (hence, it is called Low Flow NC).

Larawan 2a. Larawan ng mga Pasyente na Binibigyan ng Conventional Oxygen Therapy (COT) gamit ang nasal prongs, cannula, at face mask

Tandaan: Parehong gumagamit ng nasal cannula ang COT (o maari ring tawaging LFNC) at ang HFNC. Ang pinagkaiba lamang ng COT (o LFNC) at ng HFNC ay nagbibigay ng mas mataas na bilis ng daloy ng oxygen ang HFNC na umaabot ng 60 litro kada minuto (kaya ito tinawag na high flow NC), habang ang COT ay nagbibigay lamang ng 1 -6 litro ng oxygen kada minuto (kaya ito tinawag na low flow NC).

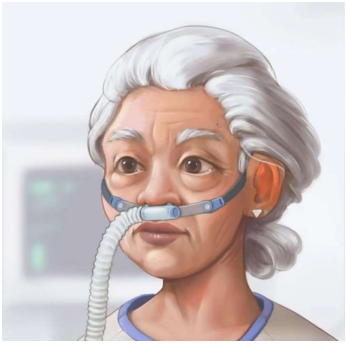

Figure 2b. Illustration of a Patient receiving High Flow Nasal Cannula (HFNC)

Note: COT (may also be called LFNC) and HFNC both use nasal cannula. The difference between COT (or LFNC) and HFNC is that HFNC provides a higher flow rate which is up to 60 liters per minute (hence, it is called High Flow NC). Meanwhile, COT can provide 1-6 liters of oxygen per minute (hence, it is called Low Flow NC).

Larawan 2b. Larawan ng Pasyente na Binibigyan ng oxygen gamit ang High Flow Nasal Cannula (HFNC)

Tandaan: Parehong gumagamit ng nasal cannula ang COT (o maari ring tawaging LFNC) at ang HFNC. Ang pinagkaiba lamang ng COT (o LFNC) at ng HFNC ay nagbibigay ng mas mataas na bilis ng daloy ng oxygen ang HFNC na umaabot ng 60 litro kada minuto (kaya ito tinawag na high flow NC), habang ang COT ay nagbibigay lamang ng 1 -6 litro ng oxygen kada minuto (kaya ito tinawag na low flow NC).

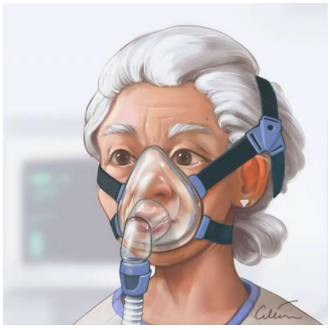

Figure 2c. Illustration of a Patient receiving either Bi-Level Positive Airway Pressure (BiPAP) or Continuous Positive Airway Pressure (CPAP)

Larawan 2c. Larawan ng Pasyente na Binibigyan ng oxygen gamit ang Bi-Level Positive Airway Pressure (BiPAP) o Continuous Positive Airway Pressure (CPAP)

The Health Professionals Alliance Against COVID-19 (HPAAC), an alliance of different medical societies, came up with a way to determine when to use non-invasive or invasive respiratory support for COVID-19 patients. This is shown in *Figure 3*.

Ang Health Professionals Alliance Against COVID-19 (HPAAC), isang samahan ng mga grupong medikal, ay gumawa ng guidelines upang matukoy kung kailan kailangang gumamit ng non-invasive o invasive respiratory support sa mga pasyente ng COVID-19 na nahihirapan sa paghinga. Makikita ito sa Larawan 3.

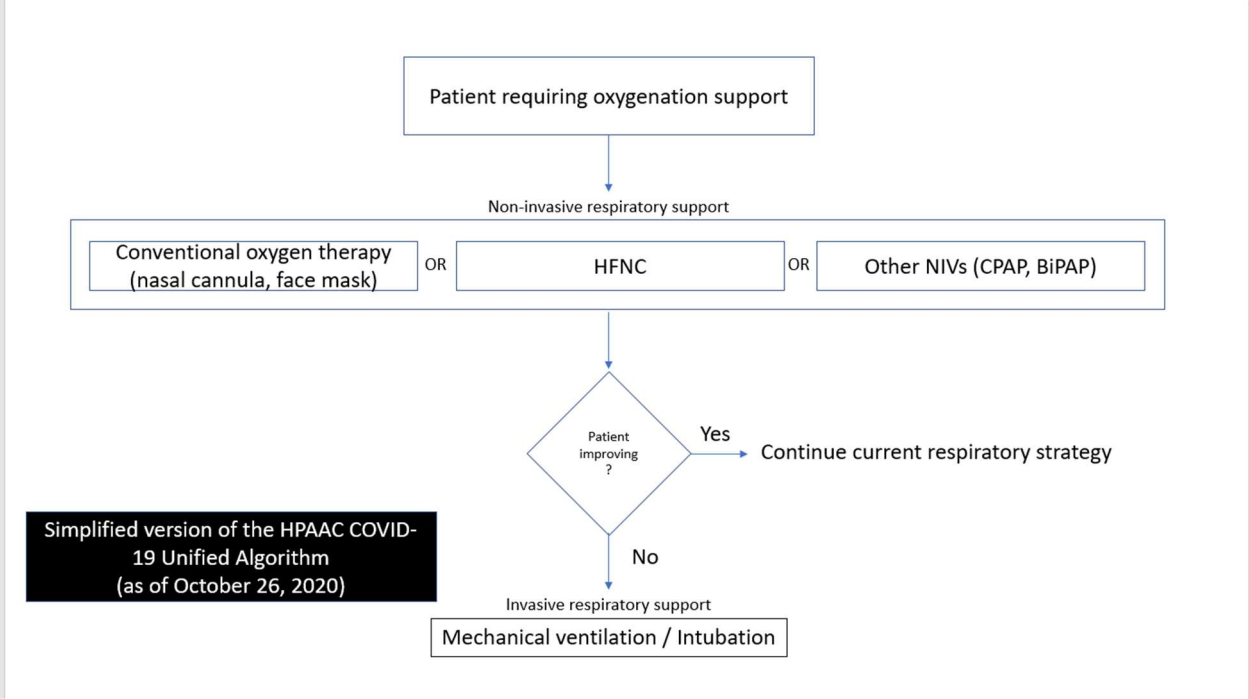

Figure 3. *HPAAC Unified Algorithm for the Management of Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Patients*

Larawan 3. Pamamaraan ng HPAAC sa Paggamot ng mga Pasyente ng COVID-19 na may AHRF

However, upon consultation with experts, it was found out that the HPAAC guidelines is not used in the actual practice. Experts from various medical societies, and private and public hospital detailed a different treatment pathway for COVID-19 patients with AHRF which uses a stepwise approach in determining which respiratory support strategy to use. This is showed in *Figure 4*.

Ngunit, ayon sa karanasan ng mga eksperto, iba ang ginagamit na paraan sa mga ospital sa pagtukoy kung ano ang nararapat na respiratory support strategy na gagamitin sa pasyente. Sila ay gumagamit ng stepwise na pamamaraan para dito. Ito ay pinapakita sa Larawan 4.

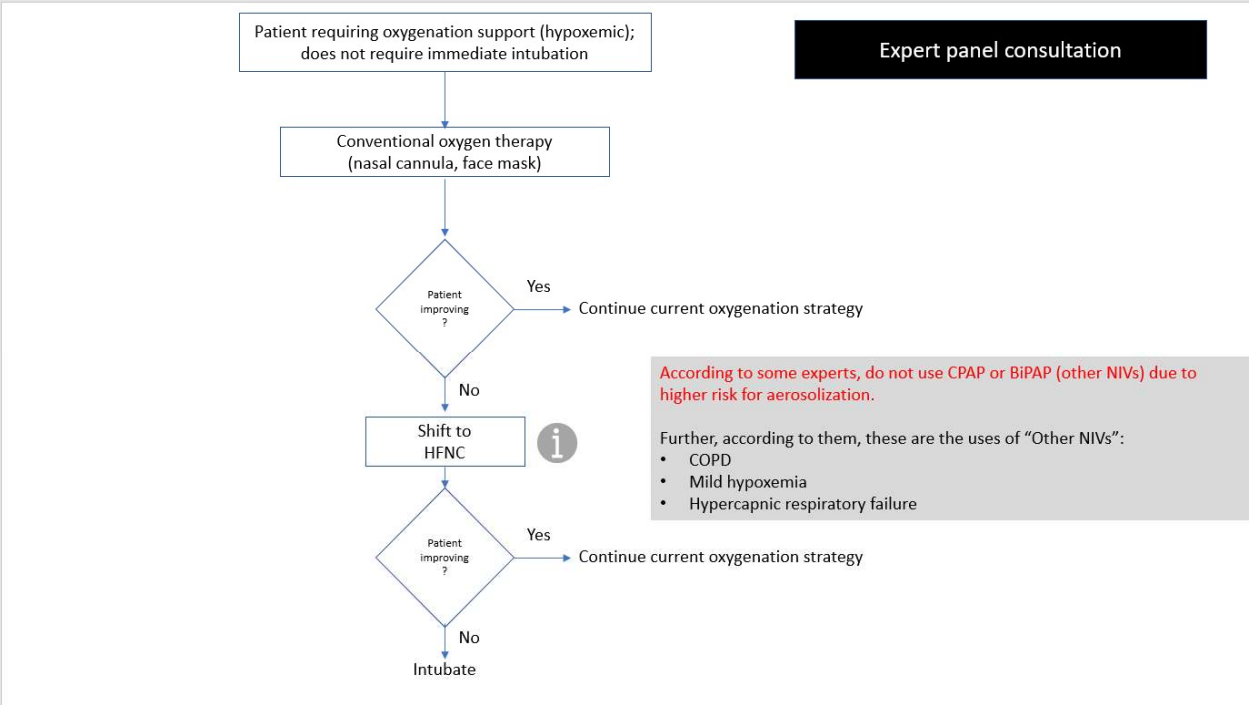

Figure 4. Algorithm used in the actual hospital setting for treatment of COVID-19 patients with Acute Hypoxemic Respiratory Failure.

Larawan 4. Pamamaraan ng mga ospital sa pagtukoy ng tamang respiratory support strategy para sa mga pasyente ng COVID-19 na may Acute Hypoxemic Respiratory Failure.

Currently, PhilHealth covers additional medical services needed by COVID-19 patients with critical pneumonia. Additionally, the Department of Health recently funded the purchase of 200 units of HFNC among other medical equipment which will be useful in addressing the needs of COVID-19 patients.

Sa kasalukuyan, kasama sa PhilHealth benefit package ang mga karagdagang serbisyong medikal na kailangan ng mga pasyenteng may malubhang pulmonya dahil sa COVID-19. Naglaan rin ng pera ang Kagawaran ng Kalusugan para sa pagbili ng 200 na yunit ng HFNC kabilang ang iba pang kagamitang pangmedikal na kakailanganin para sa gamutan ng mga pasyenteng may COVID-19.

Currently, there is not enough published evidence to show that HFNC is effective compared to other non-invasive respiratory support strategies in addressing AHRF in COVID-19 patients in terms of decreasing mortality, length of ICU stay, length of hospital stay, and preventing patient from advancing to invasive respiratory support. Since evidence on COVID-19 is rapidly evolving, clarity on the effectiveness of HFNC may be expected when ongoing local and international studies are completed.

Sa kasalukuyan, wala pang sapat na ebidensyang nagpapakita na ang HFNC para sa mga pasyente ng COVID-19 na may AHRF ay may mabisang epekto kumpara sa iba pang non-invasive respiratoty support strategy base sa dami ng pagkamatay, tagal ng pananatili sa ICU, tagal ng pananatili sa ospital, at pag-iwas na mailagay ang pasyente sa invasive respiratory support. Dahil

ang ebidensya sa COVID-19 ay mabilis na lumalabas at nadaragdagan, maaari tayong makakuha ng mas malinaw na konteksto sa pagkabisa ng HFNC kapag nakumpleto ang mga lokal at internasyonal na pag-aaral na kasalukuyang isinasagawa.

The small group discussion will zoom in on patient groups' perception and preferences when it comes to the use of *non-invasive respiratory support strategies* for COVID-19 patients with AHRF. To help in the discussion, illustrations and details of the non-invasive procedures are shown in *Table 1*.

Ang talakayang ito ay naglalayong mas alamin pa ang mga persepsyon/pang-unawa at kagustuhan ng mga grupo ng pasyente sa usapin ng paggamit ng iba't-ibang non-invasive respiratory support sa paglunas ng AHRF sa mga taong may COVID-19. Bilang gabay sa talakayang ito, ang mga detalye ukol sa iba't-ibang non-invasive respiratory support ay makikita. sa Table 1.

Table 1. Characteristics of the different non-invasive respiratory support strategies

	Non-invasive oxygenation support strategies			
	Conventional Oxygen Therapy (COT)	**High Flow Nasal Cannula (HFNC)**	**Bi-Level Positive Airway Pressure (BiPAP)**	**Continuous Positive Airway Pressure (CPAP)**
Description	The first line of treatment when not enough oxygen is delivered to the lungs. COT delivers **1-6 liters of oxygen per minute** through face masks, nasal prongs, or cannulas. This is also called Low Flow Nasal Cannula (LFNC). Note that LFNC and HFNC both use nasal cannula to deliver oxygen. However, they differ in flow rates as HFNC provides a higher flow rate compared to LFNC.	Can be used in patients when not enough oxygen is being delivered to their lungs. This procedure delivers 100% **humidified and heated oxygen** at **up to 60 liters per minute**. Note that LFNC and HFNC both use nasal cannula to deliver oxygen. However, they differ in flow rates as HFNC provides a higher flow rate compared to LFNC.	Can be used in patients when not enough oxygen is being delivered to their lungs. . **Delivers pressurized air using two pressure settings**, one for inhaling and one for exhaling	Can be used in patients when not enough oxygen is being delivered to their lungs. Delivers constant **pressurized air** using a **single pressure setting throughout.**
Advantage	• Simple and well tolerated by patients	• Decreases swelling of the airways • Improves clearance of secretions • Delivers more oxygen compared to COT	• Ideal for patients with other lung conditions such as Chronic Obstructive Pulmonary Disease (COPD)	• Prevents collapsed lung (atelectasis)

Disadvantages	• Oxygen delivery is dependent on the patient's work of breathing • Not appropriate for patients who cannot breathe on their own	• Poses risk for generation of droplets that may lead to transmission of the virus.	• Not for patients who cannot breathe on their own • Not comfortable to the patient. • Not for patients with fear of tight or crowded spaces • Increased risk for generation of droplets that may lead to transmission of the virus compared to HFNC	• Not for patients who cannot breathe on their own • Not comfortable to the patient. • Not for patients with fear of tight or crowded spaces • Increased risk for generation of droplets that may lead to transmission of the virus compared to HFNC
Estimated initial cost (Set-up cost)	Pending data	Php 8,144.00 - 10,000.00	Php 14,549.25	Php 14,549.25
Estimated cost per day	Pending data	Php 1,100.00 – 2,030.00	Php 1,840.00 - 2,860.00	Php 1,840.00 - 2,860.00

Table 1. Mga katangian ng iba't ibang non-invasive respiratory support strategies

	Non-invasive oxygenation support strategies			
	Conventional Oxygen Therapy (COT)	***High Flow Nasal Cannula (HFNC)***	***Bi-Level Positive Airway Pressure (BiPAP)***	***Continuous Positive Airway Pressure (CPAP)***

Deskripsyon	*Paunang binibigay sa pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Nakapagbibigay ng **1-6 na litro ng oxygen kada minuto** gamit ang face mask o nasal prongs o cannula.* *Ito ay tinatawag ring Low Flow Nasal Cannula (LFNC) kung ang ginamit para sa COT ay nasal cannula. Tandaan na ang LFNC at HFNC ay parehas gumagamit ng nasal cannula upang ideliver ang oxygen ngunit nagkaiba sila sa bilis ng daloy ng oxygen bilang mas mabilis ang daloy sa HFNC kumpara sa LFNC.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Nakakapagbigay ng hanggang **60 litro ng oxygen kada minuto.** Ang oxygen na naibibigay ng HFNC ay humidified para hindi makapagdulot ng panunuyo ng daluyan ng hangin. Ang oxygen na dala ng HFNC ay kapareho sa temperatura ng ating katawan.* *Tandaan na ang LFNC at HFNC ay parehas gumagamit ng nasal cannula upang ideliver ang oxygen ngunit nagkaiba sila sa bilis ng daloy ng oxygen bilang mas mabilis ang daloy sa HFNC kumpara sa LFNC.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Ito ay nagbibigay sa pasyente ng **hangin gamit ang dalawang magkaibang lakas ng pressure**, isa para sa pag-inhale at isa para sa pag-exhale.* *.*	*Maaaring ibigay sa mga pasyente kapag kulang ang oxygen na nakakarating sa baga.* *Ito ay nagbibigay sa pasyente ng **hangin** gamit ang **iisang lakas ng pressure** na tuloy-tuloy na binibigay.*
Benepisyo	• *Simple at hindi mahirap para sa pasyente*	• *Binabawasan ang pamamaga ng daluyan ng hangin ng pasyente* • *Pinapadali ang pagtanggal ng mga plema o iba pang nakabara sa daluyan ng hangin ng pasyente*	• *Mainam para sa mga pasyente ng COVID-19 at may AHRF na may iba pang kondisyon sa baga tulad ng Chronic Obstructive Pulmonary Disease (COPD)*	• *Naiiwasan ang atelectasis o ang pag-collapse ng baga*

		• *Mas maraming naibibigay na oxygen kumpara sa COT*		
Kakulangan	• *Nakadepende ang epekto nito sa kapasidad ng pasyente na mag-inhale at exhale.* • *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta).*	• *Maaring magresulta sa droplets na maaring magsanhi ng pagkalat ng virus.*	• *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta)* • *Hindi kumportable para sa pasyente* • *Hindi maaaring gamitin sa pasyenteng may takot sa masisikip o matataong espasyo.* • *Mas mataas na posibilidad na magresulta sa droplets na maaring magsanhi ng pagkalat ng virus kumpara sa HFNC.*	• *Hindi maaaring gamitin sa pasyenteng hindi kusa ang paghinga (o walang suporta)* • *Hindi kumportable para sa pasyente* • *Hindi maaaring gamitin sa pasyenteng may takot sa masisikip o matataong espasyo.* • *Mas mataas na posibilidad na magresulta sa droplets na maaring magsanhi ng pagkalat ng virus kumpara sa HFNC.*
Paunang gastos para sa pag set-up ng makina	*Wala pang datos*	*Php 8,144.00 - 10,000.00*	*Php 14,549.25*	*Php 14,549.25*
Arawang gastos	*Wala pang datos*	*Php 1,100.00 – 2,030.00*	*Php 1,840.00 - 2,860.00*	*Php 1,840.00 - 2,860.00*

Questions [SGD]

Given the information provided above, please answer the following questions. Note that there is no correct or wrong answer to these questions. Do not hesitate to ask questions and clarify points that are unclear to you.

Sa mga naibigay/naipresenta/nailahad na impormasyon, mangyari po lamang na sagutin ang mga sumusunod na tanong. Tandaan na walang tama o maling sagot sa mga katanungang ito. Huwag mag-atubiling magtanong at linawin ang mga puntong hindi malinaw sa iyo.

A. Situationer/Background on the currently available treatment of COVID 19 patients (including patients with *acute hypoxemic respiratory failure)*
    1. How has COVID-19 affected members of your community/organization?

       Kung kayo po ang tatanungin, paano naapektuhan ng COVID-19 ang mga myembro ng inyong komunidad at organisasyon?

    2. What do you think is the most difficult COVID-19 sign or symptom to manage?

       Ano sa palagay nyo naman po ang pinakamahirap na maibsan na senyales o sintomas ng COVID-19?

    3. Before this consultation, are you aware or have heard about HFNC? If yes, what did you hear about it? What are your thoughts about this health technology?

       Bago ang konsultasyong ito, may mga ideya ka ba o narinig tungkol sa HFNC? Kung oo, ano ang iyong pagkaintindi/pagkaunawa tungkol dito? Anu-ano ang iyong mga opinyon ukol dito?

B. Preference and consideration on the use of respiratory support
    1. Based on information on the different respiratory support for COVID-19 patients with AHRF (Refer to *Table 1*), arrange the following non-invasive respiratory support strategies according to which procedure you would like to be given to you first to your least preferred procedure (COT, HFNC, BiPAP, CPAP).
        i. Probing question
        What factors did you consider in selecting your least and preferred procedure?

       Base sa mga impormasyon na ibinigay tungkol sa mga respiratory support para sa mga pasyente ng COVID-19 na may AHRF (Table 1), pagsunod-sunurin ang mga ito batay sa kung alin ang iyong pinakagustong pamamaraan (COT, HFNC, BiPAP, CPAP).
        Anu-anong mga kadahilanan ang iyong kinonsidera sa pagpili ng iyong pinakagusto at hindi gustong pamamaraan ng respiratory support?

    2. Should your preferred procedure be unavailable at your hospital, how willing are you to transfer to another hospital where you can receive the service that you prefer? Will your option change if there are cost implications?

Kung ang mas gusto mong uri ng oxygen supplementation ay wala sa ospital na napuntahan mo, payag ka bang lumipat sa ibang ospital na mayroong serbisyo na nais mo? Magbabago ba ang iyong desisyon kung mayroong usapin sa gastos?

i. How much does your financial capability influence/affects the choice of procedure?

Gaano kalaki ang impluwensiya/epekto ng gastos sa pagpili mo ng oxygen supplementation?

3. How willing are you to pay for non-invasive respiratory support that has no clear/ established advantage yet over a conventional oxygen therapy, in terms of:
    i. patient mortality
    ii. length of ICU stay
    iii. length of hospital stay
    iv. escalation to intubation

    Gaano kalubag sa inyong loob ang magbayad para sa isang non-invasive respiratory support na wala pang malinaw na patunay kung ito nga ay nagbibigay ng mas malaking benepisyo sa pasyente kumpara sa conventional oxygen therapy pagdating sa:
    v. Pagkamatay ng pasyente
    vi. Haba ng pamamalagi sa ICU
    vii. Haba ng pamamalagi sa hospital
    viii. Pagiwas sa pagtutubo sa pasyente

4. In the event that using your preferred procedure will incur cost to you which is beyond your financial capacity, are you willing to loan money to pay for the procedure?
    Kung sakali na sumobra sa iyong pinansyal na kapasidad ang halagang kailangang bayaran upang matustusan ang non-invasive respiratory support strategy na iyong napili, papaya ka bang mangutang upang matustusan ito?

C. Perceived risk, benefits, and outcomes of the oxygenation support strategies
1. What are your fears/concerns/issues in using these technologies? What do you think can ease these inhibitions/fears/concerns/issues?

    Mayroon ka bang kinatatakutan/inaalala/isyu tungkol sa paggamit ng mga nabanggit na pamaraan? Ano kaya ang magpapanatag sa mga kinatatakutan/inaalala/isyu mo ukol dito?

D. Support and funding of health technologies
1. Do you think the government should cover the charges for the non-invasive respiratory support strategy that has no established advantage over conventional oxygen therapy? Why do you think so?

    Sa iyong palagay dapat bang pondohan ng gobyerno ang mga gastusin pagdating sa non-invasive respiratory support strategy kahit hindi pa malinaw sa ngayon ang lamang/ kahigitan nito sa pangkaraniwan na oxygen therapy? Bakit ito ang iyong palagay?

2. If your preferred respiratory support strategy will not be covered by PhilHealth, are you willing to pay out of pocket for this procedure? Which of the other respiratory support strategies are acceptable to you?

   Kung ang pinili mong type ng respiratory support ay hindi kasama sa babayaran ng PhilHealth, sasang-ayon ka ba sa pagbabayad nito gamit ang iyong sariling bulsa/salapi? Para sa iyo, aling mga paraan ng respiratory support ang katanggap-tanggap na bayaran gamit ang iyong sariling bulsa/salapi?

3. Would there be any practical issues (e.g., legal issues, religious reasons, and cultural beliefs) that may hinder a person from using non-invasive respiratory support?

   Mayroon ka bang naiisip na mga isyung praktikal (e.g. isyung legal, panrelihiyon, o kultural) na maaaring maging hadlang sa paggamit ng isang pasyente ng non-invasive respiratory support?

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Appendix 4. Characteristics of Excluded Studies After Full-text Review

Author (Year)	Reason for exclusion
Allardet-Servant et al. (2019)	Not the study design of interest
Bateman et al. (2016)	Not the study design of interest
Beng Leong et al. (2019)	Included studies covered by a more recent or comprehensive systematic review*
Bruni et al. (2019)	Full-text not accessible
Cheema et al. (2019)	Not the population of interest
Cortegiani et al. (2019)	Included studies covered by a more recent or comprehensive systematic review*
Ferreyro et al. (2020)	Included studies covered by a more recent or comprehensive systematic review*
Jaillette et al. (2016)	Not the study design of interest
Lee, C. et al. (2016)	Included studies covered by a more recent or comprehensive systematic review*
Lin, S. et al. (2017)	Included studies covered by a more recent or comprehensive systematic review*
Leeies et al. (2017)	Included studies covered by a more recent or comprehensive systematic review*
Maitra et al. (2016)	Included studies covered by a more recent or comprehensive systematic review*
Ni et al. (2017)	Included studies covered by a more recent or comprehensive systematic review*
Nilius et al. (2013)	Not the study design of interest
Pisani et al. (2019)	Not the population of interest
Rochwerg et al. (2019)	Included studies covered by a more recent or comprehensive systematic review*
Tinelli et al. (2019)	Included studies covered by a more recent or comprehensive systematic review*
Ongoing and future trials/studies	
Hui (2020)	Not the outcome of interest
Pavlov (2020)	Not the intervention of interest
Ricard (2020)	Not the comparator of interest
University of Milano Bicocca (2020)	Not the comparator of interest

* Note: These more recent or comprehensive systematic reviews were included in this rapid review.

Appendix 5. Critical Appraisal of Included Reviews

CRITICAL APPRAISAL
High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission
Agarwal et al., 2020

Study title (Author, Year)
High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission (Agarwal et al., 2020b)

General Information

Date form completed *(dd/mm/yyyy)*	05/11/2020
Name of person extracting data	Lara Alyssa Liban, RPh; Arwin Jerome Onda, RPh
Reference citation	Agarwal, A., et al. (2020b). High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anesth/J Can Anesth https://doi.org/10.1007/s12630-020-01740-2
Year of publication	2020
Language	☐ English. ☐ Non-English, specify: French
Notes:	

Study Characteristics

Population	1) Hospitalized and non-hospitalized patients with or without microbiologically confirmed SARS-CoV-2 infection 2) Model patient simulator 3) Critically ill adult patients due to gram-negative bacterial pneumonia
Intervention	High-flow nasal cannula (HFNC)
Comparator	1) CPAP 2) COT by face mask or nasal prongs 3) Non-rebreather mask 4) No comparator
Outcomes	1) Detection of droplets of viable airborne organisms 2) Transmission of infection associated with exposure to infected individuals receiving HFNC

Study design of included studies	1) Simulation studies 2) Crossover studies
Does the study answer your research questions/s: Our research question: *Is HFNC oxygen therapy safer than other noninvasive ventilation or conventional oxygen therapy in treating acute hypoxemic respiratory failure based on risk of aerosolization of respiratory droplets?*	Yes, it answers our research questions.

AMSTAR 2 Checklist (2017)[1–3]

- OVERALL RATING

Item	Result	
1	Yes	This systematic review has 5 critical weaknesses and 1 non-critical weakness. Domains 11, 12, and 15 are not applicable because the review did not conduct meta-analyses or quantitative synthesis of the results. Findings were reported narratively because the authors anticipated differences in study designs for the review on aerosol generation.
2	No	
3	Yes	
4	No	
5	Yes	
6	Yes	
7	No	
8	Partial Yes	
9	No	
10	No	
11	N/A	
12	N/A	
13	No	
14	Yes	
15	N/A	
16	Yes	

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	**Did the research questions and inclusion criteria for the review include the components of PICO?**	Yes. "We included all comparative and non-comparative studies that evaluated droplet dispersion or aerosolization of viable airborne organisms or transmission of infection associated with HFNC use. Anticipating the paucity of direct evidence from COVID-19 and hospitalized patients, we included all study designs and populations evaluating aerosol generation or dispersion associated with HFNC. We included studies that evaluated the following outcomes: detection of droplets or viable airborne organisms through sample analysis, or documented transmission of infection associated with exposure to infected individuals receiving HFNC, with or without comparison with an alternate ventilation modality." (page 5, par. 5)	☐ For Yes (ALL the following): Population Intervention Comparator group Outcome Timeframe for follow-up - Optional (Recommended) ☐ No
2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**	No. **Protocol** "Prior to beginning, WHO personnel reviewed and approved internal protocols for both systematic reviews; given time constraints of the commissioned reviews (seven days to completion), neither protocol was registered nor published." (page 4, par. 4) Although the authors declared that the protocols were reviewed and approved by WHO, the authors did not explicitly say that this protocol included the review questions, the search strategy, and the inclusion/exclusion criteria that they used for the systematic review. The authors also did not mention the tool used to assess risk of bias.	☐For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: review question(s) a search strategy inclusion/exclusion criteria a risk of bias assessment ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, *and* a plan for investigating causes of heterogeneity justification for any deviations from the protocol ☐ No
3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	Yes. "Anticipating the paucity of direct evidence from COVID-19 and hospitalized patients, we included all study designs and populations evaluating aerosol generation or dispersion associated with HFNC." (page 5, par. 5)	☐ For Yes, the review should satisfy ONE of the following: *Explanation for* including only RCTs OR *Explanation for* including only NRSI OR *Explanation for* including both RCTs and NRSI ☐ No
4	**Did the review authors use a comprehensive literature search strategy?**	No. **Searched at least two databases** "…using a combination of subject headings and keywords related to COVID-19, other coronaviruses, and HFNC, we conducted a comprehensive search of Ovid MEDLINE and Embase from inception to 14 May 2020." (page 5, par. 4) **Provided key word and/or search strategy**	☐For Partial Yes (all the following): searched at least 2 databases (relevant to research question) provided key word and/or search strategy justified publication restrictions ☐For Yes, should also have (all the following):

		Search strategy for review on aerosol generation is in Appendix 2 of the SR. (pages 27-30) **Justified publication restrictions** None mentioned. In terms of restriction on publication date, the authors did not justify why they decided to limit the search starting 1 January 2007. "We limited the search to literature published between 1 January 2007 and 14 May 2020." (page 5, par. 4)**Searched the reference lists/bibliographies of included studies** "…and identified one additional study through reference list screening." (page 6, par. 9) **Searched trial/study registries** None mentioned. **Included/consulted content experts in the field** "…and one additional citation suggested by an expert panelist." (page 6, par. 9) **Searched for grey literature** "To identify eligible pre-prints, we searched medRxiv from inception to 14 May 2020…" (page 5, par. 4) **Searched the reference lists/bibliographies of included studies** "…and identified one additional study through reference list screening." (page 6, par. 9)	searched the reference lists / bibliographies of included studies searched trial/study registries included/consulted content experts in the field where relevant, searched for grey literature conducted search within 24 months of completion of the review ☐ No
5	**Did the review authors perform study selection in duplicate?**	Yes. "Paired reviewers (J.B., F.M.) screened all identified citations, conducted full-text review of potentially eligible studies and screened the reference lists of reviews to identify additional eligible studies. Paired reviewers (X.Y., N.Y., X.L.) screened citations identified from the CNKI and CMJN and resolved disagreements by discussion." (page 5, par 6)	☐For Yes, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐ No
6	**Did the review authors perform data extraction in duplicate?**	Yes. "Paired reviewers (J.B., F.M.) abstracted data (study characteristics, participant characteristics, description of the intervention and control, outcomes, and general limitations in study design and conduct) independently and in duplicate using standardized data abstraction forms. A third reviewer (A.A.) resolved disagreements as necessary." (page 5, par 7)	☐For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. ☐ No

7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	No. Although the authors provided the number of studies that had undergone full-text screening but were excluded, and the number of studies excluded due to general reasons, the authors did not provide a complete list of these studies.	☐ For Partial Yes: provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: Justified the exclusion from the review of each potentially relevant study ☐ No
8	**Did the review authors describe the included studies in adequate detail?**	Partial yes. Table 5 on pages 19-20 details the characteristics of included studies. **Population** "Three simulation studies included healthy adult volunteers, and three included a model patient simulator. The crossover study included 19 critically ill adult patients who received supplemental oxygen therapy and crossed over to HFNC." **Intervention and comparators** "Three studies evaluated HFNC at 30 L_min-1, one evaluated HFNC at 40 L_min-1, and six studies evaluated HFNC at 60 L_min-1. One study compared HFNC with continuous positive airway pressure (CPAP) delivering pressures of 5–20 cmH2O, another compared HFNC with COT by face mask, two compared HFNC with COT by nasal prongs at 6 L_min-1, and one compared HFNC with non-rebreather mask with nonhumidified air at 15 L_min-1. The remaining three studies did not include an alternative oxygen administration or ventilatory support strategy as a comparator." **Outcomes** "Study outcomes included the number, diameter, evaporation rates, and velocity of exhaled aerosols, regions of high aerosol density, droplet dispersion distance, and microbial colony counts in air and surface samples." **Research designs** "Of the seven eligible studies, six were simulation studies and one was a crossover study. No studies directly evaluated risk of aerosol generation or infection transmission associated with HFNC use among patients with COVID-19." (page 7, par. 1; page 11, par 1)	☐ For Partial Yes (ALL the following): described populations described interventions described comparators described outcomes described research designs ☐ For Yes, should also have ALL the following: described population in detail described intervention in detail (including doses where relevant) described comparator in detail (including doses where relevant) described study's setting timeframe for follow-up ☐ No
9	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**	This systematic review includes only NRSI.	RCTs ☐For Partial Yes, must have assessed RoB from unconcealed allocation, *and*

			lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) ☐For Yes, must also have assessed RoB from: allocation sequence that was not truly random, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only NRSI
		No. Although the authors mentioned that there was a concern for risk of bias, they did not discuss how the risk of bias was assessed. It is therefore unknown whether the authors used a satisfactory technique in assessing the risk of bias in individual studies. "There was a concern for substantial risk of bias in design and conduct across all seven studies." (page 16, par. 1)	NRSI ☐For Partial Yes, must have assessed RoB: from confounding, *and* from selection bias ☐For Yes, must also have assessed RoB: methods used to ascertain exposures and outcomes, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only RCTs
10	**Did the review authors report on the sources of funding for the studies included in the review?**	None mentioned.	☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies ☐ No
11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	This systematic review includes only NRSI.	RCTs ☐ For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. AND investigated the causes of any heterogeneity ☐ No ☐No meta-analysis done

		No meta-analysis was done.	For NRSI ☐ For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta-analysis done
12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	No meta-analysis was done.	☐For Yes: included only low risk of bias RCTs OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. ☐No ☐No meta-analysis done
13	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**	No. The authors did not mention that they used a method or tool to assess RoB of the individual studies.	☐ For Yes: included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ☐ No
14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	Yes. "Available evidence was significantly limited by small sample sizes with healthy volunteers or simulations, and in the absence of any studies directly including COVID-19 patients or evaluating aerosolization of similar microbes, by indirectness in applying findings to SARS-CoV-2 aerosolization and COVID-19 management. Based on GRADE guidance, there was very low certainty in estimates due to inconsistency in the magnitude and direction of the association between HFNC and aerosol and droplet dispersion	☐ For Yes: There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ☐ No

		across studies, as well as indirectness and imprecision." (page 16, par. 1) "Very low certainty experimental and observational data suggested mixed findings in terms of significant droplet dispersion and aerosol generation with HFNC." (page 16, par. 2; page 17, par.1)	
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	No quantitative synthesis was performed.	☐For Yes: performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐No ☐No quantitative synthesis conducted
16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**	Yes. "All authors provided disclosures of interest to the WHO in advance of completing the systematic reviews, of which none were considered to have relevant financial conflicts of interest." (page 21, par. 5) "These rapid reviews were commissioned and paid for by the World Health Organization, and coordinated through the MAGIC Evidence Ecosystem Foundation. One co-author (Janet V. Diaz) is employed by the WHO and had no role in funding decisions for either rapid review." (page 21, par. 6)	☐For Yes: The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest ☐ No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ*. 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ*. 2017;(358).

CRITICAL APPRAISAL

The Impact of High-Flow Nasal Oxygen in the Immunocompromised Critically Ill: A Systematic Review and Meta-Analysis (Sklar et al., 2018)

Study title (Author, Year)
The Impact of High-Flow Nasal Oxygen in the Immunocompromised Critically Ill: A Systematic Review and Meta-Analysis (Sklar et al., 2018)

General Information

Date form completed *(dd/mm/yyyy)*	17 August 2020
Name of person extracting data	Arwin Jerome M. Onda, Yves Miel Zuniga
Reference citation	Sklar, M. C. M., A.Orchanian-Cheff, A.Del Sorbo, L.Mehta, S.Munshi, L. (2018). The Impact of High-Flow Nasal Oxygen in the Immunocompromised Critically Ill: A Systematic Review and Meta-Analysis. Respir Care, 63(12), 1555-1566. doi:10.4187/respcare.05962
Year of publication	2018
Language	☐ English. ☐ Non-English, specify____
Notes: This systematic review and meta-analysis focused on the immunocompromised and critically ill patients **Latest research question:** Is HFNC oxygen therapy more effective than noninvasive ventilation or conventional oxygen therapy in treating acute hypoxemic respiratory failure?	

Study Characteristics

Population	adult immunocompromised subjects undergoing HFNC for AHRF
Intervention	High-flow nasal cannula (HFNC)
Comparator	Noninvasive ventilation (NIV) or conventional oxygen therapy (COT)
Outcomes	Primary outcome: (1) Mortality at the longest available time point reported comparing HFNC to any oxygen therapy control (ie, a combination of NIV or conventional O2 therapy) Secondary outcomes:

	(1) Rate of invasive mechanical ventilation for HFNC compared to an oxygen therapy control (NIV or conventional O2 therapy) during that hospitalization
Study design of included studies	any observational studies or randomized, controlled trials (RCTs)
Does the study answer your research questions/s: Our research question: Is HFNC oxygen therapy more effective than noninvasive ventilation or conventional oxygen therapy in treating acute hypoxemic respiratory failure?	Yes, it answers the research question.

OVERALL RATING:

Item	Result
1	Yes
2	No
3	No
4	No
5	Yes
6	No
7	No
8	Partial yes
9	RCTs – yes NRSI – partial yes
10	No
11	No
12	No
13	No
14	No
15	No
16	Yes

Critically low

Domains identified with critical flaw:

- Domain 2
- Domain 4
- Domain 7
- Domain 11
- Domain 13
- Domain 15

Domains identified with non-critical weakness

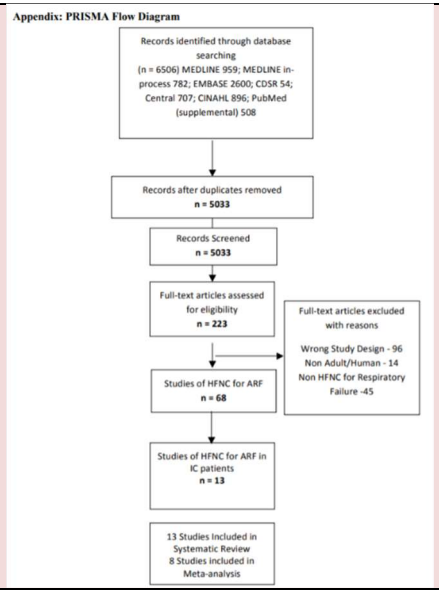
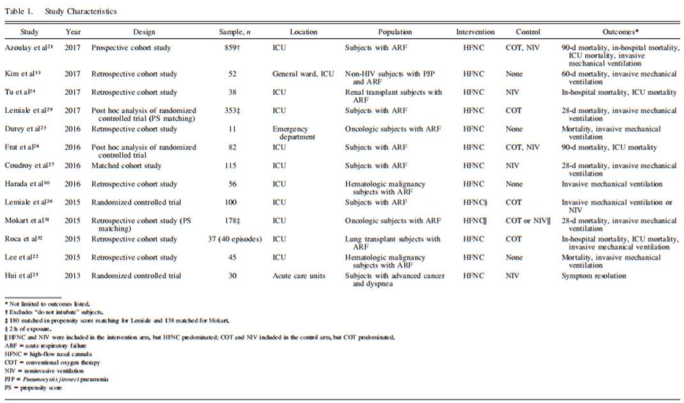
- Domain 3
- Domain 6
- Domain 10
- Domain 12
- Domain 14

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	**Did the research questions and inclusion criteria for the review include the components of PICO?**	**Population:** Yes. *"Studies of HFNC for AHRF including only immunocompromised subjects were independently selected and reviewed by reviewers."* *"We included any observational studies or randomized, controlled trials (RCTs) of adult immunocompromised subjects undergoing HFNC for AHRF."* *"We excluded pediatric studies…"* (Page 1556, Paragraph 7) **Intervention, Comparator:** Yes *"RCTs were included if HFNC was compared to NIV or conventional O2 therapy"* (Page 1556, Paragraph 7) **Outcome:** Yes *"Our primary outcome of interest was mortality at the longest available time point reported comparing HFNC to any oxygen therapy control (ie, a combination of NIV or conventional O2 therapy). Secondary outcomes included the rate of invasive mechanical ventilation for HFNC compared to an oxygen therapy control (NIV or conventional O2 therapy) during that hospitalization."* (Page 1556, Paragraph 8)	☐ For Yes (ALL the following): • Population • Intervention • Comparator group • Outcome • Timeframe for follow-up - Optional (Recommended) ☐ No
2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**	No protocol was mentioned in the study.	☐For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: • review question(s) • a search strategy • inclusion/exclusion criteria • a risk of bias assessment ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: • a meta-analysis/synthesis plan, if appropriate, *and* • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol ☐ No

3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	No explanations were provided in the study. *"We included any observational studies or randomized, controlled trials (RCTs) of adult immunocompromised subjects undergoing HFNC for AHRF."* (Page 1556, Paragraph 7)	☐ For Yes, the review should satisfy ONE of the following: • *Explanation for* including only RCTs • OR *Explanation for* including only NRSI • OR *Explanation for* including both RCTs and NRSI ☐ No
4	**Did the review authors use a comprehensive literature search strategy?**	**Searched at least 2 databases (relevant to research question)** Yes. *"The following databases were searched from inception through May 15, 2018: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Clinical Trials, and CINAHL. Additionally, we searched a clinical trials registry (http://clinicaltrials.gov) for unpublished and ongoing studies. A supplementary search was conducted in PubMed for non-MEDLINE records."* (Page 1556, Paragraph 6) **Provided key word and/or search strategy** Yes. *"At the time of the search, specific subject headings for high-flow therapy were unavailable in the databases used. The strategy was devised using an extensive list of appropriate text words and phrases. Key words were either mined from sample articles and product descriptions or generated through input from subject specialists on the team. The search was not focused on any particular population, outcome, or study type to keep it sufficiently sensitive.* (Page 1556, Paragraph 5)	☐For Partial Yes (all the following): • searched at least 2 databases (relevant to research question) • provided key word and/or search strategy • justified publication restrictions ☐For Yes, should also have (all the following): • searched the reference lists / bibliographies of included studies • searched trial/study registries • included/consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review ☐ No

		Ovid MEDLINE(R) 1946 to May Week 1 2018 **# Searches — Type** 1 (high-flow adj5 oxygen*).mp. — Advanced 2 (high-flow adj5 nasal).mp. — Advanced 3 (high-flow adj5 cannula*).mp. — Advanced 4 (high-flow adj3 therap*).mp. — Advanced 5 (high-flow adj5 humid*).mp. — Advanced 6 (high-flow adj5 hypox*).mp. — Advanced 7 (highflow adj5 oxygen*).mp. — Advanced 8 (highflow adj5 nasal).mp. — Advanced 9 (highflow adj5 cannula*).mp. — Advanced 10 (highflow adj3 therap*).mp. — Advanced 11 (highflow adj5 humid*).mp. — Advanced 12 (highflow adj5 hypox*).mp. — Advanced 13 high-floe.mp. — Advanced 14 highfloe.mp. — Advanced 15 HFOT.mp. — Advanced 16 HFNO.mp. — Advanced 17 HHFNC.mp. — Advanced 18 HFT.mp. — Advanced 19 HHHF.mp. — Advanced 20 HFNC.mp. — Advanced 21 AcuCare.mp. — Advanced 22 OptiFlow.mp. — Advanced 23 Opti-Flow.mp. — Advanced 24 Precision Flow.mp. — Advanced 25 Comfort Flo.mp. — Advanced 26 Aquinox.mp. — Advanced 27 Vapotherm.mp. — Advanced 28 PARI hydrate.mp. — Advanced 29 or/1-28 — Advanced 30 animals/ not (animals/ and humans/) — Advanced 31 29 not 30 — Advanced (Supplemental file, Pages 2-3) **Justified publication restrictions** No justifications on publication restriction were mentioned in the study. **Searched the reference lists / bibliographies of included studies** Not mentioned in the study. **Searched trial/study registries** Yes. *"Additionally, we searched a clinical trials registry (http://clinicaltrials.gov) for unpublished and ongoing studies."*	

		(Page 1556, Paragraph 5) **Included/consulted content experts in the field** Not mentioned in the study. **Where relevant, searched for grey literature** Yes. *"Additionally, we searched a clinical trials registry (http://clinicaltrials.gov) for unpublished and ongoing studies."* (Page 1556, Paragraph 5) **Conducted search within 24 months of completion of the review** Yes, the review was published the same year of the systematic search of the studies.	
5	**Did the review authors perform study selection in duplicate?**	**At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include** *"Eligibility was determined by 2 reviewers (MCS, AM). Studies of HFNC for AHRF including only immunocompromised subjects were independently selected and reviewed by reviewers. Disagreements were resolved by consensus or in discussion with a senior author (LM)."* (Page 1556, Paragraph 7)	☐ For Yes, either ONE of the following: • at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐ No
6	**Did the review authors perform data extraction in duplicate?**	**At least two reviewers achieved consensus on which data to extract from included studies** While the authors performed independent data abstraction of included studies, the method of resolution in cases of conflict was not mentioned in the study. *"Data from included studies were independently abstracted by the reviewers using a standardized data collection form. Study design, patient demographics, immunocompromised status, characteristics of oxygen delivery methods, and patient outcomes were collected. Two authors (MCS and AM) independently assessed potential sources of bias using the Cochrane Collaboration Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies."* (Page 1557, Paragraph 1)	☐ For Yes, either ONE of the following: • at least two reviewers achieved consensus on which data to extract from included studies • OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. ☐ No
7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	No. While this is the PRISMA diagram of the study, the studies excluded after full-text review weren't identified and only justifications were included.	☐ For Partial Yes: • provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: • Justified the exclusion from the review of each potentially relevant study ☐ No

			
8	**Did the review authors describe the included studies in adequate detail?**	Included studies are summarized in the table below.  Table 1. Study Characteristics (Page 1558, Table 1) **Described populations, interventions, comparators, outcomes, research designs, study's settings.** Yes. See (Page 1558, Table 1) **Described population in detail**	☐ For Partial Yes (ALL the following): • described populations • described interventions • described comparators • described outcomes • described research designs ☐ For Yes, should also have ALL the following: • described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • timeframe for follow-up ☐ No

<table>
<tr><td></td><td></td><td>Yes.
"The leading cause of immunosuppression was related to an oncologic diagnosis with a predominance of hematologic malignancy (11 of 13 studies). Two studies focused primarily on solid organ transplant. Infectious pneumonia (mainly bacterial) was the predominant cause of respiratory failure across this cohort (49–83%). Fungal infections, where reported, were found in 3–15% of cases. Opportunistic infections, particularly Pneumocystis jirovecii pneumonia, were reported in 7–24% of cases and was the primary focus of 1 study. The rates of no diagnosis for AHRF ranged from 4% to 13%." (page 1557, Paragraph 5)

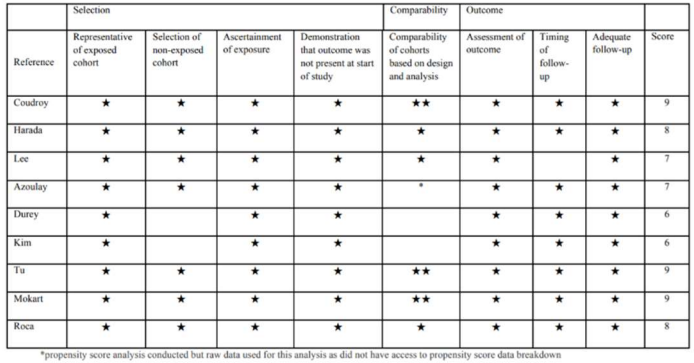
Described intervention in detail
Yes. (Page 1560, Table 3)

Described comparator in detail
Not detailed in the study.

Timeframe for follow-up
Yes, for the primary outcome mortality. (Page 1560, Table 3)</td><td></td></tr>
<tr><td>9</td><td>Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</td><td>Yes, the authors used Cochrane's risk of bias (RoB) tool.

Appendix Table 2: Risk of Methodological Bias of RCTs
<table><tr><th>Reference</th><th>Sequence Generation</th><th>Allocation Concealment</th><th>Blinding</th><th>Incomplete Outcome Data</th><th>Selective Reporting Bias</th><th>Overall Risk of Bias</th></tr><tr><td>Hui</td><td>Low</td><td>Low</td><td>High</td><td>Low</td><td>Low</td><td>Low</td></tr><tr><td>Lemiale 2015</td><td>Low</td><td>Low</td><td>High</td><td>Low</td><td>Low</td><td>Low</td></tr><tr><td>Frat</td><td>High[1]</td><td>Low</td><td>High</td><td>Low</td><td>Low</td><td>Unclear[2]</td></tr><tr><td>Lemiale 2017</td><td>High[1]</td><td>Low</td><td>High</td><td>Low</td><td>Low</td><td>Low[3]</td></tr></table>1-Graded as "high" given that these analyses were post-hoc analyses of randomized trials;2 likely low but ranked as unclear as this was a post hoc analysis of the RCT and unclear the distribution of unmeasured confounding; 3 ranked as low given propensity score matching that was implemented
(Supplemental file, Page 5)</td><td>RCTs
☐For Partial Yes, must have assessed RoB from:
• unconcealed allocation, and
• lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)
☐For Yes, must also have assessed RoB from:
• allocation sequence that was not truly random, and
• selection of the reported result from among multiple measurements or analyses of a specified outcome
☐ No

☐ Includes only NRSI</td></tr>
<tr><td></td><td></td><td>The Newcastle-Ottawa Scale for Cohort Studies was used in assessing the risk of bias for observational studies in the study. The scale is divided into three main parts:
• Selection (accounts for "confounding," "selection bias," and "methods used to ascertain exposures and outcomes")
• Comparability (accounts for "confounding")
• Outcome (accounts for "methods used to ascertain exposures and outcomes")</td><td>NRSI
☐For Partial Yes, must have assessed RoB:
• from confounding, and
• from selection bias
☐For Yes, must also have assessed RoB:
• methods used to ascertain exposures and outcomes, and
• selection of the reported result from among multiple measurements or analyses of a specified outcome
☐ No</td></tr>
</table>

		Appendix Table 3: Newcastle-Ottawa Scale for Observational Studies  (Supplemental file, Page 5) Link to the Newcastle-Ottawa Scale for Observational Studies appraisal tool: https://www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf	☐ Includes only RCTs
10	**Did the review authors report on the sources of funding for the studies included in the review?**	Sources of funding for the studies included in the review was not mentioned in the study.	☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies ☐ No
11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	**In performing the meta-analysis, the authors combined the results of the observational studies and the RCTs (i.e., did not separate the meta-analyses by study design).** **The authors justified combining the data in a meta-analysis** No justification was provided in the study. **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.** Weighted technique was mentioned in the study; however, it was not mentioned in the study if the authors adjusted for heterogeneity if present. *"For the meta-analyses, we compared HFNC to oxygen therapy control (combination of conventional O2 therapy or NIV) for our primary analysis. Meta-analysis included RCTs or any observational studies and were weighted using the inverse variance method."* *"Statistical heterogeneity among trials was assessed using the I2 statistic, defined as the percentage of total variability across studies attributable to*	RCTs ☐For Yes: • The authors justified combining the data in a meta-analysis • AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. • AND investigated the causes of any heterogeneity ☐ No ☐No meta-analysis done

		heterogeneity rather than chance, and using published guidelines for low (I2 = 25–49%), moderate (I2 = 50–74%), and high (I2 = 75%) heterogeneity." (Page 1557, Paragraph 2) **AND investigated the causes of any heterogeneity** The authors performed subgroup analyses (HFNC vs NIV, and HFNC vs COT). However, the authors did not mention whether these subgroup analyses explain the heterogeneity. Further, in the discussion portion of the study, the authors identified these parameters as sources of heterogeneity, but explanations respective to each were not provided. *"Second, heterogeneity exists with respect to the underlying immunocompromised population (eg, oncology and transplant), definitions of AHRF, indication for therapy, duration of therapy, administration of noninvasive oxygen strategies, and criteria for intubation. However, despite these differences, the signal of effect was similar across most studies."* (Page 1564, Paragraph 4)	
		The authors justified combining the data in a meta-analysis No justification was provided in the study. **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.** Weighted technique was mentioned in the study; however, it was not mentioned in the study if the authors adjusted for heterogeneity if detected to be present. *"For the meta-analyses, we compared HFNC to oxygen therapy control (combination of conventional O2 therapy or NIV) for our primary analysis. Meta-analysis included RCTs or any observational studies and were weighted using the inverse variance method."* *"Statistical heterogeneity among trials was assessed using the I2 statistic, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and using published guidelines for low (I2 = 25–49%), moderate (I2 = 50–74%), and high (I2 = 75%) heterogeneity."* (Page 1557, Paragraph 2) **AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available** Not mentioned in the study. **AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review**	For NRSI ☐ For Yes: • The authors justified combining the data in a meta-analysis • AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present • AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available • AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta-analysis done

		In performing the meta-analysis, the authors combined the results of the observational studies and the RCTs (i.e., did not separate the meta-analyses by study design).	
12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	Out of the 4 included RCTs, 3 of which were assessed to be of "low" risk of bias, and the remaining 1 study was assessed to be "unclear," although the authors added that it is likely to be of "low" risk of bias. However, the authors combined the results of RCTs and observational studies in the meta-analyses (i.e., did not separate the meta-analyses by study design). Investigation of the possible impact of RoB on summary estimates of effect was not performed by the authors.	☐For Yes: • included only low risk of bias RCTs • OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. ☐No ☐No meta-analysis done
13	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**	No. To add, the authors combined the results of RCTs and observational studies in the meta-analyses (i.e., did not separate the meta-analyses by study design). The authors did not account the RoB in individual studies when interpreting/discussing the results of the review.	☐ For Yes: • included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ☐ No
14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	In the discussion portion of the study, the authors identified these parameters as sources of heterogeneity, but explanations respective to each were not provided. *"Second, heterogeneity exists with respect to the underlying immunocompromised population (eg, oncology and transplant), definitions of AHRF, indication for therapy, duration of therapy, administration of noninvasive oxygen strategies, and criteria for intubation. However, despite these differences, the signal of effect was similar across most studies."* (Page 1564, Paragraph 4)	☐For Yes: • There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ☐ No
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	The authors did not perform statistical or graphical tests to determine and discuss the likelihood and magnitude of impact of publication bias.	☐ For Yes: • performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐ No ☐ No meta-analysis conducted
16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the**	Yes. *"The authors have disclosed no conflicts of interest."* (Page 1555)	☐For Yes: • The authors reported no competing interests OR • The authors described their funding sources and how they managed potential conflicts of interest

	review?		☐ No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ*. 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ*. 2017;(358).

CRITICAL APPRAISAL

High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis
Xu et al., 2018

Study title **(Author, Year)**
High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis (Xu, 2018)

General Information

Date form completed *(dd/mm/yyyy)*	16 Aug 2020
Name of person extracting data	Ma. Via Jucille Roderos. Arwin Jerome Onda
Reference citation	Xu, Z. L., Y.Zhou, J.Li, X.Huang, Y.Liu, X.Burns, K. E. A.Zhong, N.Zhang, H. (2018). High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis. Respir Res, 19(1), 202. doi:10.1186/s12931-018-0908-7
Year of publication	2018
Language	☐ English. ☐ Non-English, specify____
Notes: Systematic reviews including RCTS comparing HNFC vs (1) Conventional oxygen therapy (2) non-invasive ventilation and assess the efficacy of HNFC: a) as initial support strategy, and b) after extubation	

Study Characteristics

Population	adult patients with acute respiratory failure ARF was defined as the requirement for oxygen therapy to maintain peripheral capillary oxygen saturation (SpO2) > 92% or PaO2/FiO2 (P/F ratio) > 300, symptoms of respiratory distress (including tachypnea > 22 breaths/min, labored breathing, use of intercostal muscles, and/or dyspnea at rest) or using 'authors' definitions.
Intervention	High-flow nasal cannula (HFNC)
Comparator	Conventional oxygen therapy (COT) or non-invasive ventilation (NIV)
Outcomes	Primary outcomes: (1) treatment failure (2) intubation (alternatively, reintubation rate in trials comparing alternative treatments after extubation) Secondary outcomes: (1) ICU and hospital mortality (2) ICU and hospital length of stay (LOS), (3) patient comfort, (4) respiratory rate (RR), and (5) P/F ratio.
Study design of included studies	prospective RCTs

Does the study answer your research questions/s: Our research question: Is HFNC oxygen therapy more effective than noninvasive ventilation or conventional oxygen therapy in treating acute hypoxemic respiratory failure?	Yes, it answers the research questions.

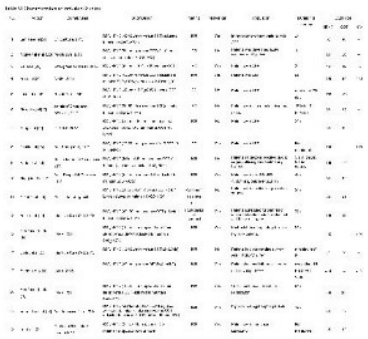
OVERALL RATING:

Item	Result	
1	Yes	Critically low Domains identified with critical flaw: Domain 2 Domain 4 Domain 7 Domain 11 Domain 13 Domain 15 Domains identified with non-critical weakness: Domain 3 Domain 10 Domain 14
2	No	
3	No	
4	No	
5	Yes	
6	Yes	
7	Yes	
8	Yes	
9	Yes	
10	No	
11	No	
12	Yes	
13	Yes	
14	No	
15	No	
16	Yes	

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	**Did the research questions and inclusion criteria for the review include the components of PICO?**	**Population, Intervention** Yes. *"We included prospective RCTs involving adult patients comparing HFNC with either COT or NIV as an initial support strategy in patients with ARF or after extubation."* (Page 2, Paragraph 2) *ARF was defined as the requirement for oxygen therapy to maintain peripheral capillary oxygen saturation (SpO2) > 92% or PaO2/FiO2 (P/F ratio) > 300, symptoms of respiratory distress (including tachypnea > 22 breaths/ min, labored breathing, use of intercostal muscles, and/or dyspnea at rest) or using 'authors' definitions.* (Page 2, Paragraph 4) **Comparator:** "The four main comparisons in our review include (a) HFNC versus COT as initial support for patients with ARF; (b) HFNC versus COT to prevent extubation failure; (c) HFNC versus NIV in patients with ARF and (d) HFNC versus NIV after extubation." (Page 2, Paragraph 6) **Outcome** *"The primary outcomes of this review were treatment failure and intubation (alternatively, reintubation rate in trials comparing alternative treatments after extubation) reflecting the efficacy of HFNC therapy (i.e., HFNC vs. COT, HFNC vs. NIV). Secondary outcomes included ICU and hospital mortality, ICU and hospital length of stay (LOS), patient comfort, respiratory rate (RR), and P/F ratio."* (Page 2, Paragraph 5)	☐ For Yes (ALL the following): Population Intervention Comparator group Outcome Timeframe for follow-up - Optional (Recommended) ☐ No
2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**	No protocol was mentioned in the study	☐For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: review question(s) a search strategy inclusion/exclusion criteria a risk of bias assessment ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, *and*

			a plan for investigating causes of heterogeneity justification for any deviations from the protocol ☐ No
3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	No explanation in the study	☐ For Yes, the review should satisfy ONE of the following: *Explanation for* including only RCTs OR *Explanation for* including only NRSI OR *Explanation for* including both RCTs and NRSI ☐ No
4	**Did the review authors use a comprehensive literature search strategy?**	**Searched at least 2 databases (relevant to research question):** *"We searched 4 databases (Pubmed, EMBASE, Scopus, and Web of Science) from electronic databases inception to September, 1st, 2018."* (Page 2, Paragraph 3) **Provided key word and/or search strategy** *"We combined the terms "high flow oxygen" with "noninvasive ventilation" or "oxygen inhalation therapy" as key words or Medical Subject Headings (MeSH) terms."* (Page 2, Paragraph 3) **Justified publication restrictions:** No justification *"We limited publications to adult patients (using author's definitions) and the English language."* (Page 2, Paragraph 2) **Searched the reference lists / bibliographies of included studies** None **Searched trial/study registries** *"We assessed the quality of all included trials based on review of published trial protocols identified on trial registration sites ID (ClinicalTrials.gov; Australia New Zealand Clinical Trials Registry, Thai Clinical Trials Registry, International Standard Randomized Controlled* *Trial Number Registry) and the details in the method section and supplements of included trials."* (Page 2, Paragraph 8) **Included/consulted content experts in the field** None **Where relevant, searched for grey literature.** None	☐For Partial Yes (all the following): searched at least 2 databases (relevant to research question) provided key word and/or search strategy justified publication restrictions ☐For Yes, should also have (all the following): searched the reference lists / bibliographies of included studies searched trial/study registries included/consulted content experts in the field where relevant, searched for grey literature conducted search within 24 months of completion of the review ☐ No

		Conducted search within 24 months of completion of the review The systematic search was done in 2018, and got published in the same year.	
5	**Did the review authors perform study selection in duplicate?**	**At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include** *"Three authors (ZX, JZ, XL), working in pairs, independently assessed study quality and disagreements were resolved by consensus"* (Page 2, Paragraph 8)	☐For Yes, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐ No
6	**Did the review authors perform data extraction in duplicate?**	**At least two reviewers achieved consensus on which data to extract from included studies** *"Three investigators (ZX, XL and JZ), working in pairs, independently reviewed and abstracted data from each retrieved article and supplement, where indicated. Discrepancies were resolved by discussion and consensus."* (Page 2, Paragraph 7)	☐For Yes, either ONE of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. ☐ No
7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	**Provided a list of all potentially relevant studies that were read in full-text form but excluded from the review** Not mentioned in the study **Justified the exclusion from the review of each potentially relevant study** Not mentioned in the study	☐ For Partial Yes: provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: Justified the exclusion from the review of each potentially relevant study ☐ No

8	**Did the review authors describe the included studies in adequate detail?**	 Timeframe for follow-up was not mentioned	☐ For Partial Yes (ALL the following): described populations described interventions described comparators described outcomes described research designs ☐ For Yes, should also have ALL the following: described population in detail described intervention in detail (including doses where relevant) described comparator in detail (including doses where relevant) described study's setting timeframe for follow-up ☐ No
9	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**	*"We appraised trial quality using the Cochrane collaboration tool for assessing risk of bias (RoB) including assessment of random sequence generation, allocation concealment, blinding (of interventions and outcome measurement or assessment), incomplete outcome data, selective reporting bias and other potential sources of bias (e.g., industry funding)."* (Page 2, Paragraph 8)	RCTs ☐For Partial Yes, must have assessed RoB from unconcealed allocation, *and* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) ☐For Yes, must also have assessed RoB from: allocation sequence that was not truly random, *and* selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only NRSI
		"We included prospective RCTs involving adult patients comparing HFNC with either COT or NIV as an initial support strategy in patients with ARF or after extubation." (Page 2, Paragraph 2)	NRSI ☐For Partial Yes, must have assessed RoB: from confounding, *and* from selection bias ☐For Yes, must also have assessed RoB: methods used to ascertain exposures and outcomes, *and*

			selection of the reported result from among multiple measurements or analyses of a specified outcome ☐ No ☐ Includes only RCTs
10	**Did the review authors report on the sources of funding for the studies included in the review?**	None	☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies ☐No
11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	**The authors justified combining the data in a meta-analysis** No justification was provided. **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.** Yes. *"We used fixed-effects models to pool data when heterogeneity was insignificant and the random effects models to pool data when significant heterogeneity was identified."* (Page 2, Paragraph 9) **AND investigated the causes of any heterogeneity** The study only mentions impact of heterogeneity on pooled results The authors reported the heterogeneity statistic but did not investigate the sources of heterogeneity. "We used the I2 statistic to evaluate the impact of heterogeneity on pooled results. An I2 value of greater than 50% indicated substantial heterogeneity" (Page 2, Paragraph 9)	RCTs ☐For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. AND investigated the causes of any heterogeneity ☐ No ☐No meta analysis done
			For NRSI ☐ For Yes: The authors justified combining the data in a meta-analysis AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw

			data when adjusted effect estimates were not available AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta analysis done
12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	The studies were pooled regardless of the risk of bias but, the authors used GRADE assessment to investigate possible impact of RoB on summary estimates of effect. *"The strength of the evidence comparing HFNC to COT in ARF patients on treatment failure and intubation rate was of low quality, whereas for the comparison of HFNC with COT in extubation patients, the evidence on treatment failure and reintubation rate was of moderate quality. When comparing HFNC to NIV, both the intubation rate in ARF and reintubation rate in extubation patients were of low quality."* (Page 5, Paragraph 2) "The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were used to assess the quality of the evidence for HFNC on rates of intubation/reintubation since GRADE assigns high, moderate, low and very low classification based on assessment of study limitations, inconsistency, indirectness, imprecision, and publication bias." (Page 3, Paragraph 1)	☐For Yes: included only low risk of bias RCTs OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. ☐No ☐No meta analysis done
13	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**	"The RCTs included were all assessed to be at low risk of bias with respect to randomization and allocation concealment except for 3 trials or which selection bias was deemed unclear." (Page 3, Paragraph 3) *"We found that HFNC (vs. COT) reduced treatment failure when used as an initial support strategy in patients with ARF. Contrary to the findings of Zhao et al., we found that compared to COT, HFNC reduced the rate of treatment failure (low quality) but not intubation rate (low quality evidence). Additionally, we found that HFNC (vs. COT) significantly reduced rates of both extubation failure (moderate quality evidence) and reintubation (moderate quality evidence) when used after extubation. Similar to studies conducted preterm infants, these findings suggests a potential clinical role for HFNC in the post extubation period [42]. Finally, compared to NIV, we found promising preliminary data in 2 trials that HFNC may reduce the rate of intubation when used as an initial support strategy. Taken together these findings support the use of HFNC versus COT as an initial support strate*	☐ For Yes: included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ☐ No

		"The strength of the evidence comparing HFNC to COT in ARF patients on treatment failure and intubation rate was of low quality, whereas for the comparison of HFNC with COT in extubation patients, the evidence on treatment failure and reintubation rate was of moderate quality." (Page 5, Paragraph 2)	
14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	None mentioned.	☐For Yes: There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ☐ No
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	*"The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria were used to assess the quality of the evidence for HFNC on rates of intubation/reintubation since GRADE assigns high, moderate, low and very low classification based on assessment of study limitations, inconsistency, indirectness, imprecision, and publication bias."* (Page 3, Paragraph 1) Only assessment using GRADE framework was done in the study In Table 2 of the study, there were footnotes referring to "potential publication bias" but the authors did not construct a funnel plot (identified as a study limitation). *"Third, we did not construct funnel plots as fewer than 10 trials were identified for each comparison."* (Page 8, Paragraph 3)	☐For Yes: performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐No ☐No meta analysis conducted X Not applicable
16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**	There is declaration of funding in the study. *The study was supported by National Natural Science Foundation of China (Grant Nos. 81490534 (NZ and HZ), 81770079(YL) and 81370177 (HZ), by National Science and Technology Major Project (No. 2017ZX10204401003), by the Chief Scientist Project of Yangcheng Scholar in Guangzhou (Grant No. 1201541642) and Canadian Institute of Health Research (FDN143285 and CCI132569). Dr. Burns holds a Merit Award from the University of Toronto, (Toronto, Canada).* (Page 8, Funding) *"The authors declare that they have no competing interests."* (Page 9, Competing Interests)	☐For Yes: The authors reported no competing interests OR The authors described their funding sources and how they managed potential conflicts of interest ☐ No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J.* 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ.* 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ.* 2017;(358).

Modified Cochrane Rapid Reviews Interim Guidance Checklist

Is high-flow nasal cannula oxygenation more effective than noninvasive ventilation or conventional oxygen therapy in treating acute hypoxemic respiratory failure in COVID-19 patients?

Villanueva, Cruz, Palileo-Villanueva (2020)

Reviewers:
Yves Miguel Zuniga
Arwin Jerome Onda

Summary checklist:

Item	Overall judgment (Yes/No)
1	No
2	No
3	Yes
4	No
5	Yes
6	No
7	Yes
8	No
9	Yes

Section/topic	#	Checklist item	Overall judgment (Yes/No)
SETTING THE RESEARCH QUESTION			
Stakeholder involvement	1	**Consult with stakeholders to ensure the research question is fit for purpose, and regarding any ad-hoc changes that may occur as the review progresses.** Not mentioned in the study.	No
PROTOCOL			
Protocol	2	**RRs preceded by a protocol and the protocol is published. Protocol development follows international standards for Rapid Reviews, such as that of WHO or Cochrane.** Presence of a protocol for conducting the rapid review was not mentioned in the study	No
INTRODUCTION			
Study objectives	3	**Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).** *"Articles on effectiveness and safety were selected based on the following inclusion criteria:* *Population: COVID-19 patients with acute hypoxemic respiratory failure* *Intervention: High-flow nasal cannula oxygen therapy* *Comparison: Noninvasive ventilation (e.g. bilevel positive airway pressure [BiPAP], continuous positive airway pressure), conventional oxygen therapy* *Outcome: failure of respiratory support (escalation to mechanical ventilation), mortality, length of hospital stay, length of ICU stay, transmission rate, nosocomial pneumonia rate* *Study designs: Any study design including systematic reviews, randomized controlled trials, observational studies, and case reports/series"* (Page 2)	Yes
METHODS			
Eligibility criteria	4	**Place emphasis on higher quality study designs (e.g. systematic reviews); consider a stepwise approach to study design inclusion.** No mention on emphasis on higher quality study designs during the inclusion of studies.	No
Search & Information sources	5	**Search performed on least one database, grey literature may or may not be searched.** Multiple databases were searched. *"Literature search for guidelines and primary studies on high-flow nasal cannula oxygenation in COVID19 patients was conducted on electronic databases (PubMed, CENTRAL, ClinicalTrials.gov, ISRCTN Registry and medRxiv), UpToDate (include society links) and Google Scholar on April 21, 2020"* (Page 2) **Common restrictions include language (may be limited to English language), region, year, publication status, study design (may limit search to SRs).** No restriction was applied on language and study design.	Yes

		"Search terms included the following and their variations: COVID-19, coronavirus, high flow nasal cannula, high flow nasal oxygen. No language restrictions were applied. Articles retrieved in languages other than English were processed using Google Translate." *"Study designs: Any study design including systematic reviews, randomized controlled trials, observational studies, and case reports/series"* (Page 2)	
Study selection	6	*Title and Abstract Screening*. **Use two reviewers for dual screen of at least 20% (ideally more) of abstracts, with conflict resolution.** No mention of title and abstract screening strategy in the article. *Full Text Screening*. **Use one reviewer to screen all included full text articles; Use a second reviewer to screen all excluded full text articles.** No mention of full-text screening strategy in the article.	No
Data extraction	7	**Limit data extraction to a minimal set of required data items OR** Yes. The authors only extracted the information that relevant to their research question, particularly on the outcomes mortality and rate of intubation. (Page 3, Table 1) **Use a single reviewer to extract data using a piloted form. Use a second reviewer to check for correctness and completeness of extracted data** No mention of data extraction strategy in the article.	Yes
Risk of bias assessment	8	**Use a valid risk of bias tool, if available for the included study designs. Limit risk of bias ratings to the most important outcomes (if applicable)** There is no critical appraisal in the review. We note that most of the studies included in the rapid review were case reports. There is a risk of bias (RoB) tool available for case series developed by Joanna Briggs Institute (University of Adelaide). As for the lone before-and-after study included (Geng, 2020), it can be appraised by risk o bias assessment tool for cohort studies. RoB tool for case reports: https://joannabriggs.org/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Case_Series2017_0.pdf	No
RESULTS			
Synthesis of results	9	**Synthesize evidence narratively OR** Yes. In pages 2-5 of the study, the authors narratively synthesized the evidence found. **Standards for conducting a meta-analysis for a systematic review also apply to a RR; consider a meta-analysis only if appropriate (i.e., studies are similar enough to pool). This will also depend on the nature of the data and information provided in the individual studies identified OR** Not applicable.	Yes

		Use a single reviewer to grade the certainty of evidence, with verification of all judgements (and footnoted rationales) by a second reviewer. In the Key Findings in Page 1, the authors have mentioned that the evidence are of "very low quality"; however, critical appraisal results of the included studies were not mentioned in the study. *"Very low-quality evidence suggest lower mortality (five observational studies) but higher failure rate of respiratory support (two observational studies) in COVID-19 patients given high-flow nasal cannula (HFNC) oxygen compared with noninvasive ventilation (NIV) and conventional oxygenation therapy."* (Page 1)	

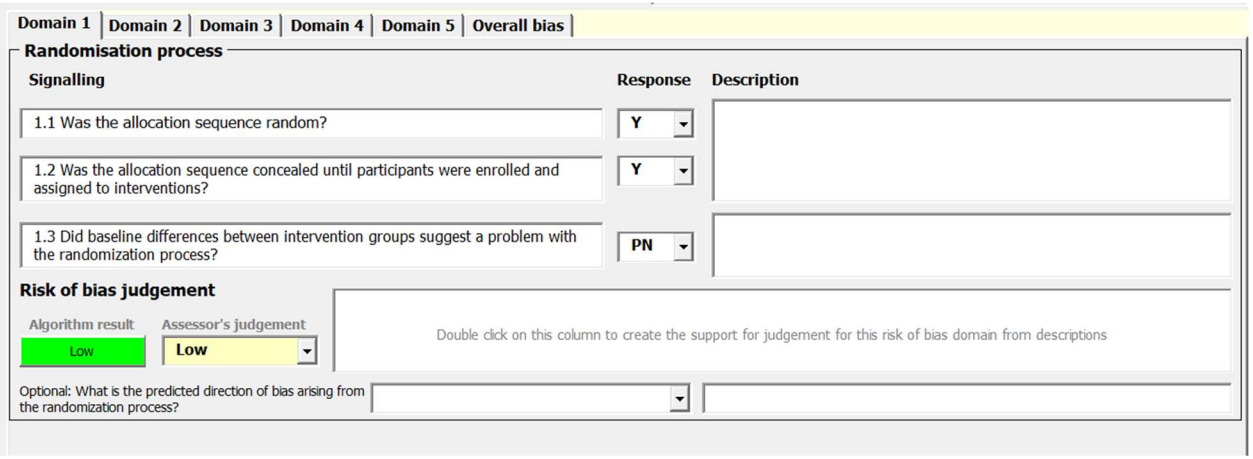
Reference: Garritty C, Gartlehner G, Kamel C, King VJ, Nussbaumer-Streit B, Stevens A, Hamel C, Affengruber L. Cochrane Rapid Reviews. Interim Guidance from the Cochrane Rapid Reviews Methods Group. March 2020.

CRITICAL APPRAISAL

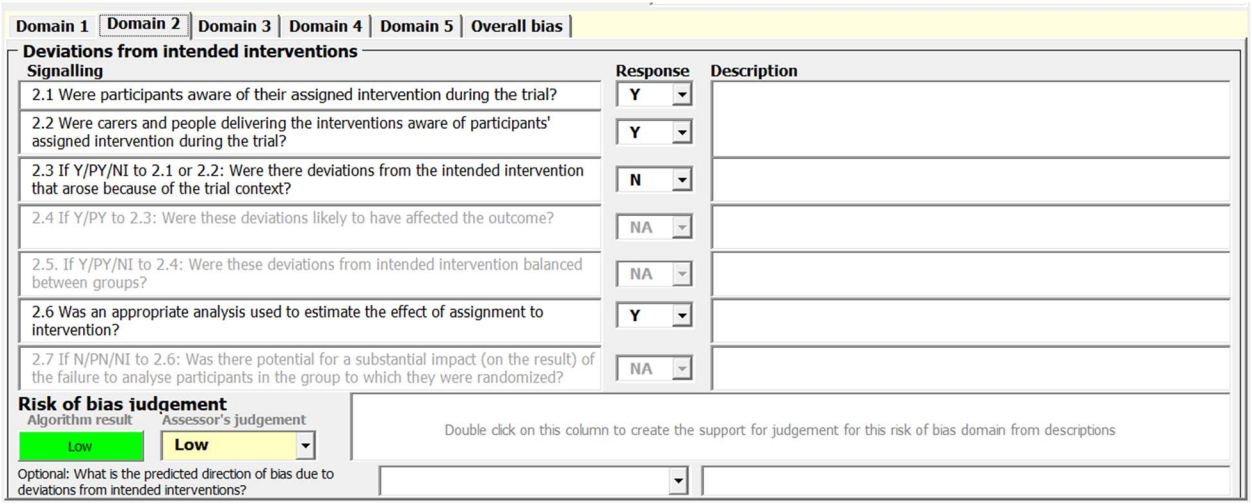
High-flow oxygen therapy through nasal cannula (HFNC) versus noninvasive positive airway pressure ventilation (NPPV) in patient with acute hypoxemic respiratory
See et al., n.d.

Critical Appraisal Tool: Cochrane RoB2 Tool (Excel version)

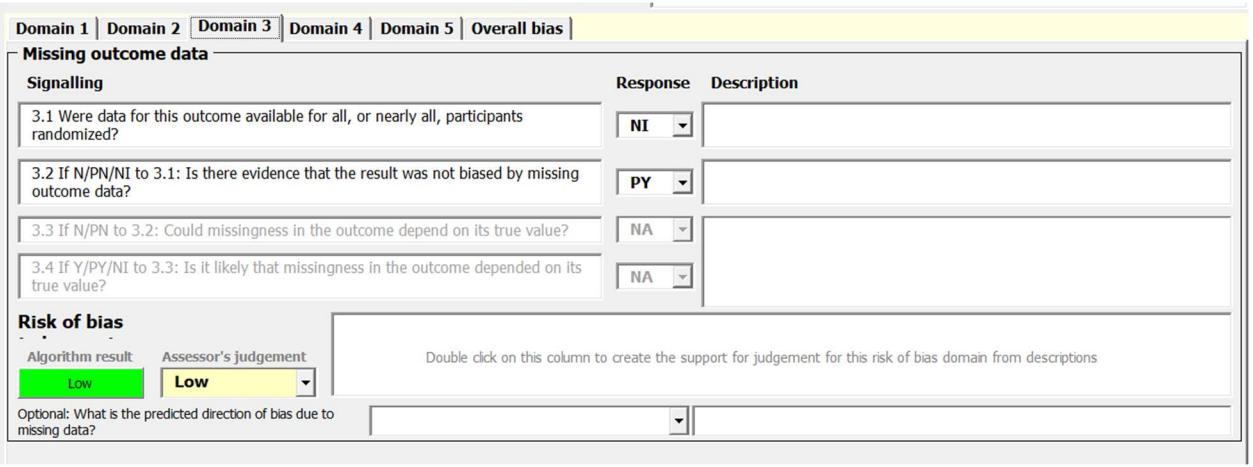
Domain 1: Randomization Process



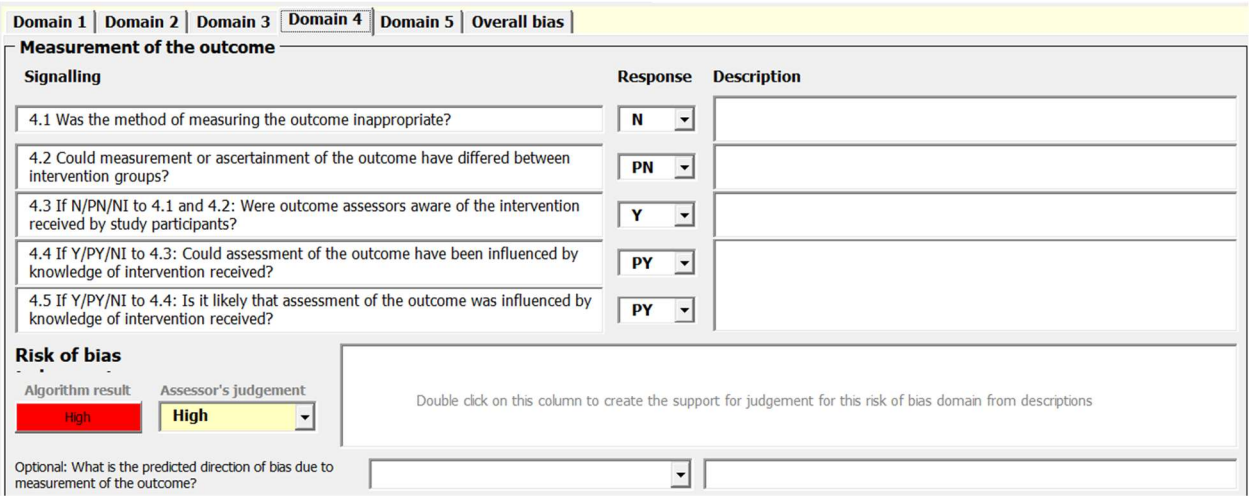
Domain 2: Deviations from intended interventions



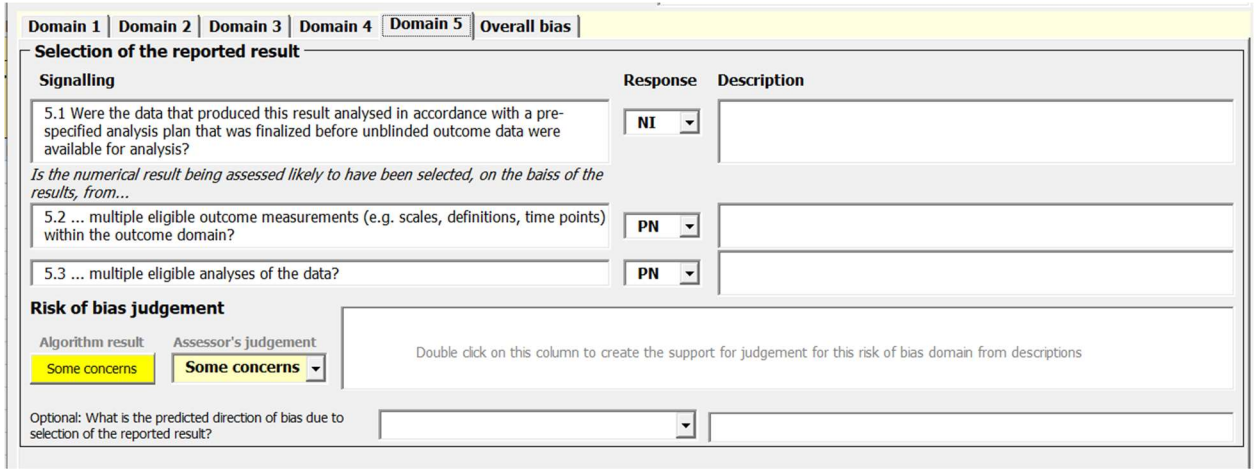
Domain 3: Deviations from intended interventions



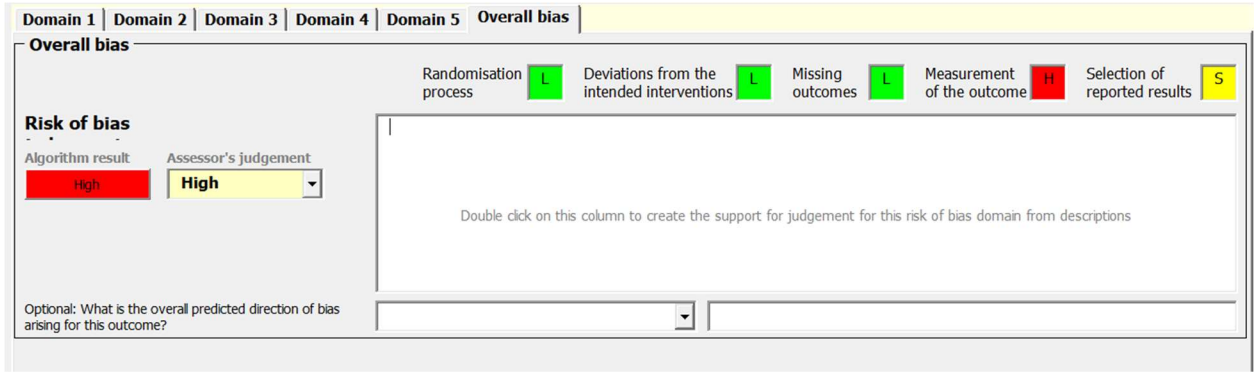
Domain 4: Measurement of the outcome



Domain 5: Selection of the reported result



Overall bias:



Appendix 6. COVID-19 treatment guidelines of organizations or countries on the use of HFNC

Legend:

Color fill of the row	Description
	Positive recommendations but with conditions for use
	Positive and negative recommendations, depending on the conditions for use
	Negative recommendation

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
WHO (as of 27 May 2020) Reference: WHO. (2020). *Clinical management of COVID-19.* Retrieved November 3, 2020, from https://www.who.int/publications/i/item/clinical-management-of-covid-19	9. Management of critical COVID-19: acute respiratory distress syndrome (ARDS) The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all cause ARDS. The following recommendations pertain to adult and paediatric patients with mild ARDS who are treated with non-invasive or high-flow nasal oxygen (HFNO) systems. 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. Remarks: 1. Patients with hypoxaemic respiratory failure and haemodynamic instability, multiorgan failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation. 2. Patients receiving a trial of HFNO or NIV should be in a monitored setting and cared for by personnel experienced with HFNO and/or NIV and capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial. 3. Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0. Paediatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow. When considering delivering HFNO or NIV outside the usual care settings, evaluating oxygen capacity is important to ensure the higher flow rates required for these devices can be maintained. See WHO Oxygen sources and distribution for COVID-19 treatment centres. 4. Because of uncertainty around the potential for aerosolization, HFNO, NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. If these interventions are performed outside of private rooms in ICUs with appropriate ventilation systems installed, then cohorting of patients requiring these interventions in designated wards will facilitate the implementation of airborne precautions, ensuring all staff entering wear appropriate PPE and adequate environmental ventilation is ensured. 23 Clinical management of COVID-19: interim guidance 5. Compared with standard oxygen therapy, HFNO may reduce the need for intubation (83). Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), haemodynamic instability, multiorgan failure or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia. Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited. 6. NIV guidelines make no recommendation on use in hypoxaemic respiratory failure (apart from cardiogenic pulmonary oedema, postoperative respiratory failure and early NIV for immunocompromized patients) or pandemic viral illness (referring to studies of SARS and pandemic influenza). Risks include delayed intubation, large

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
	tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS-CoV who receive NIV. 7. In situations where mechanical ventilation might not be available, bubble nasal CPAP may be a more readily available alternative for newborns and children with severe hypoxaemia.
Australia (as of 29 October 2020) Reference: National COVID-19 Clinical Evidence Taskforce. (2020). *Australian guidelines for the clinical care of people with COVID-19.* Retrieved November 3, 2020, from https://files.magicapp.org/guideline/03d8acae-1b4f-4624-8074-5fad1ca2adfa/published_guideline_4550-27_0.pdf	National COVID-19 clinical evidence task force Australian guidelines for the clinical care of people with COVID-19 <u>High Flow Nasal Oxygen Therapy</u> Conditional recommendation: ● Consider using High Flow Nasal Oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If HFNO is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only. Not recommended: ● Do not use HFNO therapy for patients with hypoxaemia associated with COVID-19 in shared wards, emergency department cubicles or during inter-hospital patient transfer/retrieval. <u>Respiratory management of the deteriorating patient</u> Consensus recommendation Do not delay <u>endotracheal intubation</u> and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies. Remark: Patients can deteriorate rapidly 5 to 10 days after onset of symptoms. The net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms. Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.
Canada (as of August 17, 2020) Reference: Fowler, R., Hatchette, T., Salvadori, M., Baclic, O., Volling C., Murthy, S., Emeriaud, G., Money, D., Yueng, T., Poliquin, G., Brooks, J., Decou M.L., Ofner, M. (2020). *Clinical management of patients with*	Recommendations for adult and paediatric patients w**ith ARDS who are treated with non-invasive or high flow oxygen systems** High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) should be considered. Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration. Remarks: • Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0. Paediatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow. • Compared with standard oxygen therapy, HFNO reduces the need for intubation. • Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary edema), hemodynamic instability, multiorgan failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
COVID-19: Second interim guidance. Retrieved November 3, 2020, from https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html#a71	hypercapnia • Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Evidence-based guidelines on the treatment of patients with COVID-19 with HFNO do not exist, and reports on HFNO in other coronavirus-infected patients are limited. • NIV guidelines make no recommendation for use in hypoxemic respiratory failure (apart from cardiogenic pulmonary edema and post-operative respiratory failure) or pandemic viral illness • Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS who receive NIV. • Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Patients with haemodynamic instability, multiorgan failure, or abnormal mental status should likely not receive NIV in place of other options such as invasive ventilation. • In situations where mechanical ventilation may not be available, bubble nasal CPAP may be used. for newborns and children with severe hypoxemia. • Because of uncertainty around the potential for aerosolization, HFNO, NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. If these interventions are performed outside of private rooms in ICUs with appropriate ventilation systems installed, then cohorting of patients requiring these interventions in designated wards, where possible, will facilitate the implementation of airborne precautions. All staff entering in the immediate vicinity of patients receiving potentially aerosol generating medical procedures must wear PPE appropriate for the procedures.
China (as of 18 August 2020) Reference: National Health Commission (2020). *Diagnosis and Treatment Protocol for COVID-19 Patients*, Tentative 8th ed. Retrieved November 3, 2020, from http://regional.chinadaily.com.cn/pdf/DiagnosisandTreatmentProtocolforCOVID-19Patients(Tentative8thEdition).pdf	Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition) • Severe patients with PaO2/FiO2 ratio < 300 mmHg should receive oxygen therapy with nasal cannula or face mask immediately, under close monitoring for 1 to 2 hours. For those without improvement in respiratory distress and/or hypoxemia, high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) should be used. • Patients with PaO2/FiO2 ratio < 200 mmHg should be treated with HFNC or NIV. Prone positioning for > 12 hours per day should be performed in patients treated with HFNC or NIV, if not contraindicated. Some patients have a high risk of treatment failure with HFNC or NIV, and they should be closely monitored for any deterioration of symptoms and signs. If the patient does not improve after a short trial (1 to 2 hours), as suggested by refractory hypoxemia, tachypnea, or excessive tidal volume or inspiratory effort, especially after prone positioning, this usually indicates treatment failure with HFNC or NIV, and invasive mechanical ventilation should not be delayed.
Indonesia (as of 13 July 2020) Reference: Ministry of Health Indonesia. (2020). *PEDOMAN PENCEGAHAN DAN*	(Text in Indonesian, translated via Google Translate) Management of Critically Ill COVID-19 Confirmed Patients a. Management of Hypoxemic Respiratory Failure and ARDS High-Flow Nasal Oxygen (HFNO) or non-invasive ventilation (NIV), only in patients with respiratory failure hypoxemia, and these patients should be closely monitored to assess clinical deterioration.

<table>
<tr><th>Organization/ countries (date of last update of the guideline), Reference</th><th>Specific guidelines on HFNC</th></tr>
<tr><td>PENGENDALIAN. Retrieved November 3, 2020, from https://covid19.go.id/storage/app/media/Protokol/REV-05_Pedoman_P2_COVID-19_13_Juli_2020.pdf</td><td>The HFNO system can provide up to oxygen flow with 60 L / min and FiO2 to 1.0; pediatric circuit generally only reaches 15 L / min, so a lot the child needs an adult circuit to provide flow sufficient. Compared with standard oxygen therapy, HFNO reduces the need for intubation.

Patients with hypercapnia (exacerbation of lung disease obstructive, cardiogenic pulmonary edema), no hemodynamics stable, multi-organ failure, or decreased consciousness shouldn't use HFNO, even though it's data latest mention that HFNO might be safe on mild-moderate hypercapnia patients without worsening.

Patients with HFNO should be monitored by staff trained and experienced intubation endotracheal because when the patient has worsening sudden or no improvement (within 1 hour) then an immediate intubation was carried out.

Current guidelines evidence-based about HFNO does not exist, and reports on HFNO in MERS patients is still limited.≤

Recent publications indicate that the HFNO system and NIV using an interface that conforms to face so that no leakage will reduce risk of airborne transmission when the patient is expiring.

Endotracheal intubation should be performed by trained personnel and experienced with attention to transmission alertness airborne Patients with ARDS, especially young children, are obese or pregnant, can desaturate rapidly during intubation. The patient was pre-oxygenated prior to intubation with Oxygen Fraction (FiO2) 100% for 5 minutes, via facemask with air bag, bag-valve mask, HFNO or NIV and then continued with intubation.</td></tr>
<tr><td>Japan (as of 3 Sep 2020)

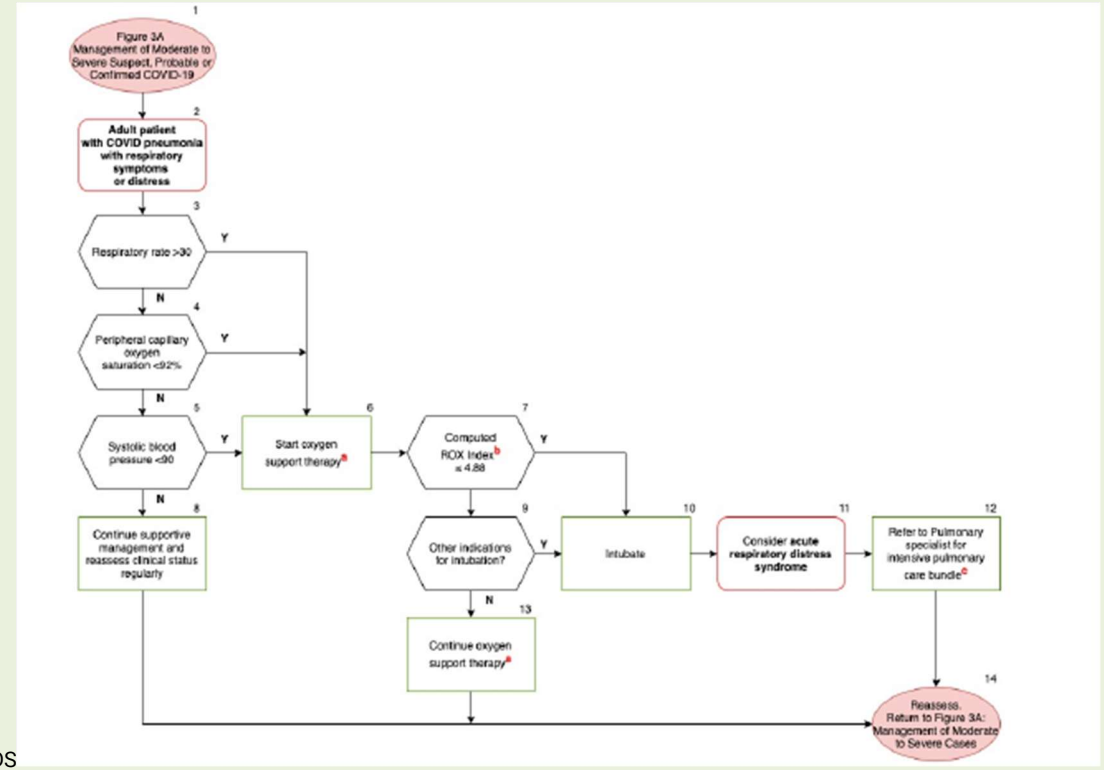
Reference:
Ministry of Health, Labour and Welfare. (2020). COVID-19 Infection: Medical Guidance version 3. Retrieved November 3, 2020 from https://www.mhlw.go.jp/content/000668291.pdf</td><td>(Translated from Japanese via Google Translate)
4. Severity classification (criteria evaluated by healthcare professionals)
<table>
<tr><th>Severity</th><th>Saturated Oxygen Level</th><th>Clinical Status</th><th>Point of Care</th></tr>
<tr><td>Moderate II With Respiratory Failure</td><td>$SpO_2 \leq 93\%$</td><td>Oxygen Administration Required</td><td>● Estimate the cause of respiratory failure
● Consider transferring to a facility that can provide advanced medical care
● Nasal High Flow, CPAP, etc.
● Avoid use as much as possible and aerosol
● Suppress the occurrence</td></tr>
</table>
[Moderate II respiratory failure]

● If SpO 2 ≥ 93% cannot be maintained even after O_2 administration with an oxygen mask, steroids or REM Consider the transition to artificial respiration while observing the effects of decibir.

* Note: Not recommended due to the risk of environmental pollution, but at this stage, usually a mask with a reservoir (10 ~ 15 L / min), Nasal high flow and non-invasive positive pressure ventilation are considered. Because aerosol is generated, there is a risk of nosocomial infection, it is desirable to use a negative pressure private room. When using high flow, set it to 30 ~ 40 L / min and make sure that the cannula is in the nasal cavity. Wear a surgical mask to suppress aerosol generation.

3. 3. COVID-19 Artificial breathing strategy for critically ill patients</td></tr>
</table>

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
	3) Selection of respiratory therapy considering the impact on the environment ● Low flow oxygen therapy is the first choice ● Do not use high flow oxygen therapy or non-invasive positive pressure ventilation ● If the esophageal pressure can be measured, intubate the internal pressure amplitude> 15 cm H 2 O as soon as possible. ● Use a bacterial filter for the gas inlet / outlet of the ventilator ● Use an artificial nose or an artificial nose with a filter function for heating and humidifying the artificial respiration circuit. ● Use a closed system for tracheal suction ● Do not perform work with a high risk of aerosol generation as much as possible.
Malaysia (as of September 30, 2020) Reference: Ministry of Health Malaysia. (2020) *CLINICAL MANAGEMENT OF CONFIRMED COVID-19 CASE IN ADULT AND PAEDIATRIC*. Retrieved November 3, 2020 from http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_2e_Clinical_Management_For_Confirmed_COVID-19_in_Adult_and_Paed.28.09.20.pdf	CLINICAL MANAGEMENT OF CONFIRMED COVID-19 CASE IN ADULT AND PAEDIATRIC General Care for Child with COVID-19 Oxygen supplementation ● Use low flow nasal cannula (LFNC) oxygen ● If children are still hypoxic despite LFNC, high flow nasal cannula (HFNC) can be used, limit it preferably in negative pressure isolation room (since use of HFNC is considered aerosol generating procedure (AGP) ● Routine blood gases are not needed. This can be done if despite HFNC, children appear to require further respiratory support. Capillary blood gas may be used to look at pH and pCO2. In critical (stage 5) cases, additional pressure and ventilatory support may be required including intubation. • Stage 5 (critical stage) where there is new or increased need for noninvasive/invasive ventilatory support, sepsis, multiorgan failure, or rapidly worsening clinical status. General Care for Adult with COVID-19 In general, the use of non-invasive ventilation is discouraged when managing patient with COVID-19. However, recent publications suggest that newer High Flow Nasal oxygenation (HFNO) and Non-invasive ventilation (NIV) systems with good interface fitting do not create widespread dispersion of exhaled air.

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
Philippines -HPAAC (as of 26 October 2020) Reference: Healthcare Professionals Alliance of the Philippines. (2020). *UNIFIED COVID-19 ALGORITHMS*. Retrieved: November 5, 2020	Recognition and Management of ARDS  Footnotes: a Oxygen support therapy - Oxygen support via facemask or non-rebreather mask with hepa filter - May use HFNC at 40-60 L/min overlapped with a face mask and NIPPV in a single negative pressure room - Maintain O_2St > 92 % Can start bag-mask ventilation (BMV) with HEPA Filter
UK - NHS England (as of 8 April 2020)	High flow nasal oxygen or similar high flow devices should be avoided: ● local maximum oxygen outlet delivery limitations preclude widespread use

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
Reference: UK NHS. (2020). *Clinical guide for the management of critical care for adults with COVID-19 during the coronavirus pandemic.* Retrieved November 3, 2020, from https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0216_Specialty-guide_AdultCritiCare-and-coronavirus_V2.pdf	• risk of environmental viral contamination is unknown but may be higher than invasive mechanical ventilation
US - NIH (as of 17 July 2020) Reference: US NIH. (2020). *Oxygenation and Ventilation.* Retrieved November 3, 2020, from https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/	Oxygen and ventilation For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting. 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). (Moderate recommendation) For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation. Infection control The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room (AIIR), when available (AIII). • Aerosol-generating procedures include endotracheal intubation and extubation, sputum induction, bronchoscopy, mini-bronchoalveolar lavage, open suctioning of airways, manual ventilation, unintentional or intentional ventilator disconnections, noninvasive positive pressure ventilation (NIPPV) (e.g., bilevel positive airway pressure [BiPAP], continuous positive airway pressure [CPAP]), cardiopulmonary resuscitation, and, potentially, nebulizer administration and high-flow oxygen delivery. Caution regarding aerosol generation is appropriate in situations such as tracheostomy and proning, where ventilator disconnections are likely to occur.
EU	No guidelines found.
Singapore	No guidelines found.
South Korea	No guidelines found.

Organization/ countries (date of last update of the guideline), Reference	Specific guidelines on HFNC
Thailand	Thailand Ministry of Public Health website not accessible as of November 3, 2020.
Vietnam (as of March 25, 2020) Ministry of Health – Vietnam (2020) *Decision No. 1344 / QD-BYT issuing guidelines for diagnosis and treatment of acute respiratory infections caused by SARS-CoV-2 (COVID-19)*. Retrieved November 3, 2020 from: http://soyte.namdinh.gov.vn/Uploads/2020/3/8/30/Cv_so_1344-QD_-_BYT_ban_hanh_Huong_dan_Chan_doan_va_dieu_tri_viem_duong_ho_hap_cap_do_SARS-CoV-2_20200326112359634630.pdf	(Translated from Vietnamese via Google Translate) Treatment of respiratory failure Treatment of critical respiratory distress & ARDS - When the hypoxia condition cannot be improved by measures of oxygen, $SpO_2 \leq 92\%$, or / and respiratory exertion: may consider assigning a high flow oxygen to breathe through the nose mountings (High Flow Nasal Oxygen), CPAP, or mechanical ventilation does not penetrate BiPAP. - Non-invasive mechanical ventilation method is not used in patients with severe debilitating disease, organ failure, and clinical symptoms. -Carefully follow and closely monitor patients to detect signs of failure to timely intervention. If the lack of oxygen does not improve with measures of respiratory support is not intrusive, need endotracheal intubation, and invasive mechanical ventilation.