PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Effect of high-flow nasal cannula oxygen vs. standard oxygen on mortality in patients with acute hypoxemic respiratory failure: protocol for a multicentre, randomised controlled trial (SOHO).

Authors

Frat, Jean-Pierre; Coudroy, Remi; Quenot, Jean-Pierre; GUITTON, Christophe; Badie, Julio; Gacouin, Arnaud; Ehrmann, Stephan; Demoule, Alexandre; Jarousseau, Fabien; Carteaux, Guillaume; Rigaud, Jean Philippe; Reignier, Jean; Sedillot, Nicholas; Contou, Damien; Beloncle, François; Daubin, Cédric; Dureau, Anne-Florence; Fatah, Abdelhamid; Besse, Marie-Catherine; Ferre, Alexis; Turbil, Emanuele; MERDJI, Hamid; Galerneau, Louis-Marie; Lacombe, Béatrice; Richard, Jean-Christophe; Romen, Antoine; Delbove, Agathe; Prat, Gwenael; Lautrette, Alexandre; Colin, Gwenhaël; Soum, Edouard; Bourdin, Gaël; Hernández, Gonzalo; Ragot, Stéphanie; Thille, Arnaud W

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Lim, Daniel Yan Zheng**
Affiliation	**Singapore General Hospital**
Date	**14-Jan-2024**
COI	**Nil**

Thank you for the opportunity to review this paper. It is a protocol for a randomised control trial comparing HFNC to standard oxygen therapy in patients with AHRF. The primary outcome is 28 day mortality.

Some points for consideration of the study team

1. Population

- COVID-19 patients are excluded. How will the study team confirm that there is no COVID-19 e.g. PCR vs antigen testing? is one-off test good enough to exclude early COVID-19?

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- Only patients with pulmonary infiltrate are included. Those with cardiac failure are excluded. There is no mention about vascular causes of hypoxemia e.g. pulmonary embolism. Is it the study team intention to study primarily patients with pneumonia? If so then perhaps this should be more prominently stated rather than presenting it a general study of AHRF

- Patients without insurance coverage will be excluded. Does this affect equitability of recruitment?

2. Randomisation

- No queries

3. Intervention

- No queries

4. Analysis Plan

- No queries

5. Safety and Data Monitoring

- There is no safety monitoring board. While there may exist no legal obligation to do so in the investigators' country, it is good that potential harm is minimised in study patients. In particular, the COVID-19 literature suggests that patients who do not respond to HFNC, delay of intubation may results in poorer outcomes including mortality. The duration of HFNC a patient is on prior to intubation (i.e. delay of intubation) that is associated with poorer outcomes is not universally agreed, but there are reports of the critical time being <48h. For this study, 48h on HFNC is allowed.

Bime C et al. Delayed intubation associated with in-hospital mortality in patients with COVID-19 respiratory failure who fail heated and humified high flow nasal canula. BMC Anesthesiology volume 23, Article number: 234 (2023)

Kang BJ et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med

. 2015 Apr;41(4):623-32.

Lopez-Ramirez et al. Delayed mechanical ventilation with prolonged high-flow nasal cannula exposure time as a risk factor for mortality in acute respiratory distress syndrome due to SARS-CoV-2. Intern Emerg Med. 2023; 18(2): 429–437.

Reviewer **2**

Name **Kim, Won Young**

Affiliation **University of Ulsan College of Medicine, emergency medicine**

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Date	**04-Feb-2024**
COI	**no**

This study protocol applies to non-COVID-19 patients, excluding COVID-19 patients from the SOHO-COVID randomized clinical trial, which investigated whether high-flow nasal cannula oxygen, compared to standard oxygen therapy, could reduce mortality in COVID-19 patients, as published in NEJM in 2022. Other than excluding COVID-19 patients, the study protocol remains consistent with previous research and is well-designed. There are some aspects that need to be modified and improved.

In the intervention section of the methods, it was mentioned that the experimental group, using high-flow oxygen, would set the FiO2 to maintain SpO2 between 92% and 96% for at least 48 hours. It would be better to provide a more detailed explanation of how the FiO2 settings in the high-flow oxygen groups are titrated. For instance, specifying a reduction of FiO2 by 5 if SpO2 is maintained above 98% for more than 1 hour could be considered.

In the sample size calculation, an estimated mortality rate for the control groups using standard oxygen was specified as 18%. However, in the discussion section, a rate of 30% was mentioned. The two values show a significant difference, so it would be advisable to provide a consistent value.

It appears to me, comparing other study from ICU, HTNC study should be evaluated short-term outcome, for example death within 72 hours or intubation within 72 hours. How about adding short-term outcome in SOHO trial, if possible.

Reviewer	**3**
Name	**Depuydt , Pieter**
Affiliation	**Ghent University Hospital, Department of Intensive Care Medicine**
Date	**15-Apr-2024**
COI	**I have no competing interests on behalf of this study.**

The protocol as presented for the SOHO study is appropriate in all respects.

However, I would like to suggest two additional aspects or analyses/inform whether the study protocol would allow for the following analyses.

Do the authors plan a cost-benefit analysis, as the use of high-flow oxygen therapy comes with a considerable additional cost (humidifier systems and medical gasses).

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Bayesian analysis may offer advantages over the frequentist approach planned in the study protocol, i.a. the incorporation of the prior beliefs and the prior knowledge gathered thus far (there exists already quite some literature on this topic), and the handling of covariates (underlying immunosuppression and cause of the hypoxemic respiratory failure). Will the statistical plan, sample size and collection of data allow this?

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Daniel Yan Zheng Lim, Singapore General Hospital

Comments to the Author:

Thank you for the opportunity to review this paper. It is a protocol for a randomised control trial comparing HFNC to standard oxygen therapy in patients with AHRF. The primary outcome is 28 day mortality.

Some points for consideration of the study team

Population

- COVID-19 patients are excluded. How will the study team confirm that there is no COVID-19 e.g. PCR vs antigen testing? is one-off test good enough to exclude early COVID-19?

Response:

You are correct that we excluded patients with acute respiratory failure due to COVID-19, the reason being that the ancillary SOHO-COVID trial showing a decreased risk of intubation with high-flow nasal oxygen compared with standard oxygen was known in this setting (Frat et al. JAMA 2022). Similar to the ancillary study, the diagnosis of COVID-19 infection is left to the discretion of the physician, and in most cases the diagnosis is ruled out via reverse transcriptase–polymerase chain reaction test from a nasopharyngeal swab, which tests for multiple viral infections including COVID-19. However, a pulmonary infection occurring after a COVID-19 infection can be included in the study, when the cause of ARF is considered to be due not to COVID-19 infection but rather to this second infection.

- Only patients with pulmonary infiltrate are included. Those with cardiac failure are excluded. There is no mention about vascular causes of hypoxemia e.g. pulmonary embolism. Is it the study team intention to study primarily patients with pneumonia? If so

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then perhaps this should be more prominently stated rather than presenting it a general study of AHRF

Response:

Thank you for this relevant comment.

Patients with cardiogenic pulmonary edema are excluded from the study, as NIV is the reference treatment and a treatment by oxygen only is not ethical, while a treatment based on HFNC has not been shown to be superior over NIV. The SOHO trial aims to include all causes of ARF with pulmonary infiltrates (bilateral or not), and not only those due to pneumonia. The causes of ARF will be collected in the e-CRF as described in ARDS, with common risks (Fergusson at al. Intensive care medicine 2012) including pneumonia, extrapulmonary sepsis, pulmonary contusion, aspiration… or no common risks including connective tissue disease, hypersensitivity pneumonitis, drug-induced pneumonia (Gibelin et al. Intensive care medicine 2016)… Of course, the most frequent cause of hypoxemic ARF in non-immunosuppressed patients is likely to be pneumonia in more than 70% of cases (Frat et al. NEJM 2015).

To emphasize this point, we added the following footnote to Table 1 to specify the causes of respiratory failure collected in the e-CRF: “Reasons for respiratory failure will be collected in the e-CRF and classified as follows: Pneumonia (community-acquired pneumonia, hospital-acquired pneumonia and documentation if available), other common risks (Non-pulmonary sepsis, Aspiration of gastric content, Major trauma, Pulmonary contusion, Inhalation injury, Severe burns, Non-cardiogenic shock, Drug overdose, Multiple transfusions or transfusion-associated acute lung injury, Pancreatitis, Drowning), other non-common risks (Connective tissue disease, Small-vessel vasculitis, Hypersensitivity pneumonitis, Drug-induced pneumonia, Hematology malignancy, Solid Tumor, Lymphangitic carcinomatosis, Organizing pneumonia, Diffuse alveolar hemorrhage, Massive hemoptysis, No etiology identified, Other).”

- Ferguson N, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive care medicine 2012;38:1573-82.

- Gibelin A, Parrot A, Maitre B, et al. Acute respiratory distress syndrome mimickers lacking common risk factors of the Berlin definition. Intensive care medicine 2016;42:164-72.

- Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. The New England journal of medicine 2015;372:2185-96.

- Patients without insurance coverage will be excluded. Does this affect equitability of recruitment?

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Response:

Thank you for this ethical comment, but French law (article L1121-11, code de la santé publique) stipulates that patients without insurance coverage cannot participate in any trial, so it appears in the exclusion criteria.

Randomisation, Intervention, Analysis Plan

- No queries

Safety and Data Monitoring

- There is no safety monitoring board. While there may exist no legal obligation to do so in the investigators' country, it is good that potential harm is minimised in study patients. In particular, the COVID-19 literature suggests that patients who do not respond to HFNC, delay of intubation may result in poorer outcomes including mortality. The duration of HFNC a patient is on prior to intubation (i.e. delay of intubation) that is associated with poorer outcomes is not universally agreed, but there are reports of the critical time being <48h. For this study, 48h on HFNC is allowed.

- Bime C et al. Delayed intubation associated with in-hospital mortality in patients with COVID-19 respiratory failure who fail heated and humified high flow nasal canula. BMC Anesthesiology volume 23, Article number: 234 (2023)

- Kang BJ et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015 Apr;41(4):623-32.

- Lopez-Ramirez et al. Delayed mechanical ventilation with prolonged high-flow nasal cannula exposure time as a risk factor for mortality in acute respiratory distress syndrome due to SARS-CoV-2. Intern Emerg Med. 2023; 18(2): 429–437.

Response:

This comment is very important and we agree that delaying intubation is likely to have a negative impact on the prognosis of patients.

Although a Safety Review Board is not required for this trial in France, all adverse events will be collected and reported to the coordinating center and serious adverse events must be reported within 24 hours. To reduce the risk of delayed intubation, we defined pre-specified intubation criteria in the study design, and they were discussed and accepted by all the investigators prior to the start of the study. These are described in the section “Events during allocated oxygen strategy”. In our previous studies, these criteria were well-respected and

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resulted in no statistical difference among the oxygen strategies in time to intubation (Frat et al. NEJM 2015; Frat et al. JAMA 2022).

To clarify the duration and the management of oxygen strategies, we modified the sections "Control group: standard oxygen" and "Experimental group: high-flow oxygen" as follows:

"In the standard oxygen group, oxygen is delivered through facemask or non-rebreathing mask, with oxygen flow set at 10 L/min minimum, adjusted to maintain SpO2 between 92 and 96%, for at least 48 hours until the patient recovers, unless the patient requires intubation..."

"In the high-flow nasal oxygen group, high-flow nasal cannula oxygen therapy is delivered with oxygen applied through a heated humidifier (MR850, Fisher and Paykel Healthcare) continuously through large-bore binasal prongs, with a gas flow rate of at least 50 litres per minute and FiO2 titration of 5-10% set to maintain SpO2 between 92 and 96% (Optiflow or Airvo-2, Fisher and Paykel Healthcare; or dedicated ICU-ventilator with high-flow oxygen therapy option) for at least 48 hours until the patient recovers, unless the patient requires intubation..."

- Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. The New England journal of medicine 2015;372:2185-96.

- Frat JP, Quenot JP, Badie J, et al. Effect of High-Flow Nasal Cannula Oxygen vs Standard Oxygen Therapy on Mortality in Patients With Respiratory Failure Due to COVID-19: The SOHO-COVID Randomized Clinical Trial. Jama 2022;328:1212-22.

Reviewer: 2

Dr. Won Young Kim, University of Ulsan College of Medicine

Comments to the Author:

This study protocol applies to non-COVID-19 patients, excluding COVID-19 patients from the SOHO-COVID randomized clinical trial, which investigated whether high-flow nasal cannula oxygen, compared to standard oxygen therapy, could reduce mortality in COVID-19 patients, as published in NEJM in 2022. Other than excluding COVID-19 patients, the study protocol remains consistent with previous research and is well-designed. There are some aspects that need to be modified and improved.

Thank you for that very kind general comment.

In the intervention section of the methods, it was mentioned that the experimental group, using high-flow oxygen, would set the FiO2 to maintain SpO2 between 92% and 96% for at least 48 hours. It would be better to provide a more detailed explanation of how the FiO2

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settings in the high-flow oxygen groups are titrated. For instance, specifying a reduction of FiO2 by 5 if SpO2 is maintained above 98% for more than 1 hour could be considered.

Response:

Thank you for this comment, we modified this section as follows: “In the high-flow nasal oxygen group, high-flow nasal cannula oxygen therapy is delivered with oxygen applied through a heated humidifier (MR850, Fisher and Paykel Healthcare) continuously through large-bore binasal prongs, with a gas flow rate of at least 50 litres per minute and a FiO2 titration of 5-10% set to maintain SpO2 between 92 and 96% (Optiflow or Airvo-2, Fisher and Paykel Healthcare; or dedicated ICU-ventilator with high-flow oxygen therapy option) for at least 48 hours until the patient recovers, unless the patient requires intubation...”

In the sample size calculation, an estimated mortality rate for the control groups using standard oxygen was specified as 18%. However, in the discussion section, a rate of 30% was mentioned. The two values show a significant difference, so it would be advisable to provide a consistent value.

Response:

We agree with this comment, indeed 30% is the maximum mortality reported in previous studies in patients with acute hypoxemic respiratory failure treated with standard oxygen.

Consequently, we modified the first paragraph of the discussion as follows: “While standard oxygen is the first-line therapy for acute hypoxemic respiratory failure, high rates of intubation failure reaching 50% (ranging from 30 to 50% and mortality ranging from 11 to 30% have led to the development of other oxygenation strategies…”

It appears to me, comparing other study from ICU, HTNC study should be evaluated short-term outcome, for example death within 72 hours or intubation within 72 hours. How about adding short-term outcome in SOHO trial, if possible.

Response:

Thank you for this point of discussion. Although it is controversial, some authors (and reviewer 1) have reported a possible risk of delayed intubation with HFNC use and an association with higher risk of mortality, as previously reported with NIV. Therefore, we chose to assess risks of intubation and mortality at day 28. However, Kaplan-Meier curves of the cumulative probability of intubation and mortality can provide an estimate of these risks during observation time.

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- Kang BJ et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015 Apr;41(4):623-32.

- Lopez-Ramirez et al. Delayed mechanical ventilation with prolonged high-flow nasal cannula exposure time as a risk factor for mortality in acute respiratory distress syndrome due to SARS-CoV-2. Intern Emerg Med. 2023; 18(2): 429–437.

- Carrillo A, Ferrer M, Gonzalez-Diaz G, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 2012;186:1279-85.

Reviewer: 3

Prof. Pieter Depuydt , Ghent University Hospital

Comments to the Author:

The protocol as presented for the SOHO study is appropriate in all respects.

Thank you for that very kind general comment.

However, I would like to suggest two additional aspects or analyses/inform whether the study protocol would allow for the following analyses.

- Do the authors plan a cost-benefit analysis, as the use of high-flow oxygen therapy comes with a considerable additional cost (humidifier systems and medical gasses).

Response:

We share this concern with the reviewer, but unfortunately we do not plan to do such an analysis, and it bears mentioning that most of the participating centers and ICUs in France and Spain already use HFNC.

- Bayesian analysis may offer advantages over the frequentist approach planned in the study protocol, i.a. the incorporation of the prior beliefs and the prior knowledge gathered thus far (there exists already quite some literature on this topic), and the handling of covariates

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(underlying immunosuppression and cause of the hypoxemic respiratory failure). Will the statistical plan, sample size and collection of data allow this?

Response:

Thanks for this interesting comment. Although we do not rule out doing a Bayesian analysis, we preferred to initially adopt a frequentist approach so as to make the results easier to read. Another reason is that we will include a large population, which will strengthen the validity of the results. In addition to providing results that are easier for readers to interpret, in contrast to Bayesian analysis a frequentist approach highlights the magnitude of the treatment effect.

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Kim, Won Young**
Affiliation medicine	**University of Ulsan College of Medicine, emergency**
Date	**26-Aug-2024**
COI	**no**

All the Author's response are appropriate. I hope SOHO trial goes well.

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