## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | High-flow nasal oxygen therapy alone or with noninvasive ventilation in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure: the randomised multicentre controlled FLORALI-IM protocol |
| **AUTHORS** | Coudroy, Rémi; Frat, Jean-Pierre; Ehrmann, Stephan; Pène, Frédéric; Terzi, Nicolas; Decavèle, Maxens; Prat, Gwenael; Garret, Charlotte; Contou, Damien; Bourenne, Jeremy; Gacouin, Arnaud; Girault, C; Dellamonica, Jean; Malacrino, Dominique; Labro, Guylaine; Quenot, Jean-Pierre; Herbland, Alexandre; Jochmans, Sébastien; Devaquet, Jérôme; Benzekri, Dalila; Vivier, Emmanuel; Nseir, Saad; Colin, Gwenhaël; Thévenin, Didier; Grasselli, Giacomo; Assefi, Mona; Guerin, Claude; Bougon, David; Lherm, Thierry; Kouatchet, Achille; Ragot, Stéphanie; Thille, Arnaud |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Lim Beng Leong<br>Emergency Department<br>Ng Teng Fong Hospital<br>Singapore |
| **REVIEW RETURNED** | 05-Mar-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | Dear authors:<br>I thank the editor for allowing me to review this study protocol. The study of HFOT vs HFOT and NIV in acute hypoxemic respiratory failure among immunosuppressed patients is clinically relevant and important.<br><br>The protocol is well written but have a few comments to state.<br>1. Since there are prior studies of HFOT+NIV vs HFOT alone in acute hypoxemic respiratory failure in immunosuppressed patients, the introduction did not state why your trial is urgently needed in the context of these prior studies. The authors have stated the problems with these studies in the discussion but should briefly summarize the limitations of these studies in the introduction to capture readers' attention to the urgent need of this trial. The chief reasons are prior studies have problems with NIV settings and their analysis are post-hoc.<br><br>2. The authors should state any stopping guidelines for the trial or their data monitoring committee. This can allow readers to be aware that the investigators value the safety of the participants.<br><br>3. It would also be good if the authors can state whether they anticipated any problems in the conduct of the trial. A brief summary will do. |

| | |
|---|---|
| **REVIEWER** | Jun Duan<br>Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, P. R. China |
| **REVIEW RETURNED** | 11-Mar-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is a multicenter RCT aimed to compare the HFOT vs. HFOT + NIV in immunocompromised patients. As few RCTs provided the oxygenations by HFOT or NIV in immunocompromised patients, this study is very important for clinical staffs to select oxygenation strategy, whether the outcome is positive or not. I have several concerns as follows.<br><br>1 Urgent need for intubation is one of the exclusion criteria. How to judge the urgent need for intubation? A checklist is encouraged.<br>2. The volume of secretions and cough strength should be considered. HFOT is better than NIV on humidification. NIV in weak cough patients may result in apnea.<br>3. How to deal with NIV intolerance. Excluded these patients?<br>4 The NIV ventilator is various. Dedicated ventilator results in less asynchrony than ICU ventilators (Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest.2012V142N2:367-376). How to deal with this problem?<br>5. In acute hypoxemic respiratory failure, the transpulmonary pressure is very high. It is difficult to control low tidal volume ventilation in these patients. How to assure the VT 6-8 ml/Kg? Whether sedation is permitted?<br>6 Interface in NIV is diverse. Helmet is better than face mask (JAMA. 2016, 315(22): 2435-41). The same interface for NIV patients is easy to realize. |

| | |
|---|---|
| **REVIEWER** | Bushra Mina<br>Lenox Hill Hospital<br>new York, USA |
| **REVIEW RETURNED** | 13-Mar-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | 1) need better definition of the "immunosuppressed state. For example remitting malignancy might not be an immunosupressed state<br>2) Randamization up to 6 hours from inclusion may delay treatment in whatever form and may affect outcome. need to be shortened in my opinion<br>3) set clinical criteria to define improvement after initiation of NIV in HFOT with NIV arm<br>4) evaluate the etiology of ARF on outcomes |

| | |
|---|---|
| **REVIEWER** | Laveena Munshi<br>Interdepartmental Division of Critical Care Medicine<br>University of Toronto<br>Canada |
| **REVIEW RETURNED** | 22-Mar-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | RESEARCH QUESTION/OBJECTIVES:<br>• This is an important and timely question. It focuses on a more “severe” cohort of acute hypoxemic respiratory failure within immunocompromised patients.<br>• It addresses many physicians concerns about the historic evidence suggesting benefit of NIV which are based upon 2 |

| | |
|---|---|
| | outdated RCTs for which the approach to acute respiratory failure with (diagnosis and management) has evolved. As the authors outline, there has been observational data across the immunocompromised and non-immunocompromised subgroups that show that NIV failure is associated with an increased mortality.<br>• In the secondary analysis of Lung Safe focused on immunocompromised patients, NIV was used as first line in approximately 21% of patients with ARDS – which highlights the importance of achieving greater clarify on this subject. My only suggestion would be to consider reporting this high frequency of NIV use across this population (Cortegiani et al ICM 2018)<br>• I understand that this study is nearly complete based upon their timeline outlined therefore this review is limited to reviewing the rationale and clarity of the methodology<br><br>ABSTRACT:<br>• The abstract presents a balanced overview of the issues.<br><br>DESIGN:<br>POPULATION:<br>• Pragmatically many physicians institute HFNC or NIV when patients are failing continuous oxygen therapy. INVICTUS and the HIGH trial demonstrated that NIV vs. continuous oxygen therapy (COT) and HFNC vs COT do not reduce intubation rates/mortality. However, the inclusion criteria of saturation <90 or paO2 <60 on room air may not reflect the use of these non-invasive currently. The inclusion criteria in the design of this study represents a “more severe” subset of early hypoxemic respiratory failure compared to the previous trials (P/F <300 on 10L/min)<br>• This study is novel in that its focused on the immunocompromised population<br>• Exclusion criteria are appropriate.<br><br>INTERVENTION/COMPARATOR:<br>• The authors have protocolized the study intervention and comparator.<br>• Through their design they attempt to address one of the previous theories for harm associated with NIV application (injurious ventilation) through their more rigorous protocol focusing on (1) a more protective ventilatory approach, and (2) minimizing interruption of alveolar recruitment through alternating NIV with HFNC<br>• It is novel that the authors propose a criteria for weaning after 48 hours of exposure<br>A few questions for consideration/clarity<br>• It would be useful for the authors to include their titration of FIO2 in the HFNC group. Is there a threshold of FiO2 where they drop the flow? How do they approach patients who cannot tolerate flows of 60L/min?<br>• I do not see a protocol outlined on the approach to managing NIV. MY presumption is that if the tidal volumes are greater than 8cc/kg they will just reduce the driving pressure. If they continue to be high – will they just maintain CPAP through NIV?<br><br>OUTCOME:<br>• Primary and secondary outcomes are appropriate<br><br>ANALYSIS/METHODS: |

| | |
|---|---|
| | • Methods described clearly, thoroughly and appropriate. I have no major concerns as the statistical approach is sound<br>• I have a few minor inquiries outlined below. While they will conduct an intention to treat analysis, is there a plan to also per protocol analysis?<br>• I think it would be important as there may be the risk of the following deviations and having clarity as to whether these deviations impact the utility would be important:<br>o Patients who are randomized to NIV+HFNC who do not tolerate 12 hours of NIV<br>o Patients who have tidal volumes that are outside of the lung protective protocol (although this is limited by the inability to measure tidal volumes in the HFNC group) but a comparison of those who achieved <8cc/kg via NIV against HFNC would be interesting<br>o Patients who may not tolerate 60L/min of flow through HFNC<br>o Patients who may cross over within the first 48 hours at the discretion of the physician<br>o Patients who, after the 48 hour time period, cross over into the alternative arm and have a sustained exposure to that arm (I am not sure the risk of this based upon the practice across these institutions)<br>• Sample size calculation<br>o Their projected 28-day mortality rates are 35% mortality in the NIV arm; and an anticipated 15% 28-day mortality benefit from HFNC are sufficiently justified in their protocol despite the differences across INVICTUS (lower NIV mortality – patients less severely ill) and HIGH (higher HFNC mortality – but a subset of these patients died before intubation).<br>o A 15% difference is a reasonable target and the same size appears feasible<br>• A very minor point – what is the nutrition practice at these institutions with respect to nutrition on HFNC and NIV? Is it anticipated that most of these patients will remain NPO because of the concern about intubation? Or, do they allow HFNC pts to eat but not NIV? After a few hours if stable, will they allow HFNC to eat or continue NG tube feeds? Will that be the practice between breaks of NIV?<br><br>LIMITATIONS AND DISCUSSION:<br>• Clear, no issues |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Lim Beng Leong
Institution and Country: Emergency Department
Ng Teng Fong Hospital
Singapore
Please state any competing interests or state ‘None declared’: None declared
Dear authors:
I thank the editor for allowing me to review this study protocol.
The study of HFOT vs HFOT and NIV in acute hypoxemic respiratory failure among immunosuppressed patients is clinically relevant and important.

The protocol is well written but have a few comments to state.
1. Since there are prior studies of HFOT+NIV vs HFOT alone in acute hypoxemic respiratory failure in immunosuppressed patients, the introduction did not state why your trial is urgently needed in the context of these prior studies. The authors have stated the problems with these studies in the discussion but should briefly summarize the limitations of these studies in the introduction to capture readers' attention to the urgent need of this trial. The chief reasons are prior studies have problems with NIV settings and their analysis are post-hoc.
Answer: Thank you for this comment. As suggested, we added the limitations of prior studies on HFOT with NIV and HFOT alone in the Introduction section.
2. The authors should state any stopping guidelines for the trial or their data monitoring committee. This can allow readers to be aware that the investigators value the safety of the participants.
Answer: Unfortunately, we did not plan interim analysis and a data safety monitoring committee was not required by the ethics committee. This decision may have been supported by the European and American recommendations on the use of NIV in this clinical setting and by the absence of data suggesting harm from HFOT according to previously published studies. However, each oxygenation strategy was optimised to offer the best management for acute respiratory failure and criteria for intubation were clearly specified allowing for avoidance of the deleterious effects of a delayed intubation whatever the group of randomization.

3. It would also be good if the authors can state whether they anticipated any problems in the conduct of the trial. A brief summary will do.
Answer: Participating centres were activated after a live meeting or teleconferences to explain the study protocol and to answer questions from investigators. Moreover, the principal investigator was reachable by phone or email 24/7 over the study period to answer questions from investigators on the study protocol and facilitate adherence to the protocol. Furthermore, all participating centres have been progressively monitored according to the inclusion rate by experienced clinical research associates to ensure the validity of inclusion and exclusion criteria, data collected and outcomes. Therefore, deviations to the protocol were immediately reported and correction measures had to be taken by investigators from participating centres. Additionally, newsletters were sent periodically to all participating centres to highlight common issues encountered by some centres and to keep them updated on the inclusion rate. Therefore, we tried to anticipate as much as we could any problem in the conduct of the trial.

Reviewer: 2
Reviewer Name: Jun Duan
Institution and Country: Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, P. R. China
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below
This is a multicenter RCT aimed to compare the HFOT vs. HFOT + NIV in immunocompromised patients. As few RCTs provided the oxygenations by HFOT or NIV in immunocompromised patients, this study is very important for clinical staffs to select oxygenation strategy, whether the outcome is positive or not. I have several concerns as follows.

1. Urgent need for intubation is one of the exclusion criteria. How to judge the urgent need for intubation? A checklist is encouraged.
Answer: Urgent need for intubation included respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, or severe hypoxemia defined as SpO2 lower than 90% or PaO2 lower than 50 mm Hg despite maximal oxygen support. The Exclusion criteria section has been modified accordingly.

2. The volume of secretions and cough strength should be considered. HFOT is better than NIV on humidification. NIV in weak cough patients may result in apnea.
Answer: We agree that secretions and cough strength influence NIV failure rates especially during the post-extubation period or in patients with pneumoniae (Hong et al. Noninvasive ventilation failure in pneumonia patients ≥ 65 years old: The role of cough strength. J Crit Care 2018;44:149). However, to our knowledge, weak cough and abundant secretions are not undeniably recognized factors of NIV failure in de novo acute respiratory failure. In you cohort, (Duan et al. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive care medicine 2017;43:192-9), these 2 factors were not retained in the HACOR score for intubation that included heart rate, acidosis, consciousness, oxygenation, and respiratory rate. Therefore, we did not plan to assess cough and secretions in our study and assume that randomization will balance the proportion of patients with no or weak cough in both arms. In our study, the vast majority of centres carry out NIV using ICU ventilators with a heated humidifier and thus humidification is exactly the same with HFOT and NIV.

3. How to deal with NIV intolerance. Excluded these patients?
Answer: These patients will not be excluded in the intention-to-treat analysis. Investigators are encouraged to modify NIV settings (pressure-support, PEEP, minimizing leaks, inspiratory trigger and cycling, interface switch) to improve NIV tolerance. The management of NIV intolerance has been added in the Control group section. As suggested by Reviewer#4, a per protocol analysis will be performed in patients without protocol deviation (i.e. those who will receive NIV at least 12 hours per day during the first 2 days), excluding those who could not tolerate NIV or received less than 12 hours of NIV per day.

4 The NIV ventilator is various. Dedicated ventilator results in less asynchrony than ICU ventilators (Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest.2012V142N2:367-376). How to deal with this problem?
Answer: It is true that dedicated ventilators may be associated with lower incidence of patient-ventilator asynchronies than ICU ventilators as shown in the study you mentioned above (Carteaux et al. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest 2012;142:367-76). However, the incidence of asynchronies were very low in this study with an asynchrony index of 0.5% using dedicated NIV ventilators and lower than 3% in median using ICU ventilators. Although this difference was statistically significant, its clinical relevance is uncertain and whether the use of dedicated ventilators results in lower intubation rate than ICU ventilators is unknown. We recently performed a systematic review of the literature comparing the incidence of intubation among patients treated with NIV for de novo acute respiratory failure in randomised trials according to the protocol to carry out NIV. The incidence of intubation was not different between patients treated with dedicated and ICU ventilators (Coudroy et al. Ann. Intensive Care 2019;9(Suppl 1):P-55). The reference has been added in the Control group section.

5. In acute hypoxemic respiratory failure, the transpulmonary pressure is very high. It is difficult to control low tidal volume ventilation in these patients. How to assure the VT 6-8 ml/Kg? Whether sedation is permitted?
Answer: It is true that NIV could result in very high transpulmonary pressures that could generate high expired tidal volumes. For patients with expired tidal volumes > 8 ml/kg of predicted body weight, we proposed investigators to reduce pressure-support or to increase PEEP levels, 2 settings associated with a decreased transpulmonary pressure in patients under pressure-support ventilation. However, we did not encourage the use of sedation and analgesia given that Muriel and colleagues reported a 5-fold increase in NIV failure rate using such a strategy (Muriel et al. Impact of sedation and analgesia during noninvasive positive pressure ventilation on outcome: a marginal structural model causal analysis Intensive Care Med 2015;41:1586). As suggested by Reviewer#4, a post-hoc analysis will be

performed in patients without protocol deviation (i.e. those whom expired tidal volume will be below 8 mL/kg of predicted body weight).

6 Interface in NIV is diverse. Helmet is better than face mask (JAMA. 2016, 315(22): 2435-41). The same interface for NIV patients is easy to realize.
Answer: It is true that the study from Patel and colleagues found better outcomes in patients treated with NIV with a specific Helmet than with facial mask in a small sample-sized monocenter trial. However, these encouraging results have not been confirmed in a large multicenter randomised trial yet. Moreover, it is unclear whether the benefits reported are due to the NIV interface or to the NIV settings (lower pressure support and higher PEEP in the Helmet arm than in the facial mask arm). Furthermore, most of centres participating to our trial were not familiar with the use of this kind of Helmet. Indeed, the management of patients treated with NIV through a Helmet requires experienced physicians and nurses, careful monitoring, specific pressure support settings, and does not allow the monitoring of expired tidal volumes. For these reasons, we did not require participating centres to use Helmet in the HFOT with NIV arm. However, the interface used for NIV will be collected. Depending on the number of patients treated with a Helmet, a subgroup analysis will be performed according to the type of NIV interface used. A paragraph has been added in the Predetermined Subgroup Analysis section.

Reviewer: 3
Reviewer Name: Bushra Mina
Institution and Country: Lenox Hill Hospital
New York, USA
Please state any competing interests or state ‘None declared’: None declared

1. Need better definition of the “immunosuppressed” state. For example, remitting malignancy might not be an immunosuppressed state.
Answer: It is true that we planned to include patients with a wide range of immunosuppression and that patients with remitting solid cancer might not be immunocompromised. For this reason, we decided to include only patients with active solid cancer. For patients with remitting hematologic malignancy, immunotherapy has persistent effects and it is not clear whether and when they have a full immune recovery. Moreover, recent large cohort studies or trials in immunocompromised critically ill included likewise patients with remitting malignancy for less than 5 years (Lemiale et al. JAMA 2015; Azoulay et al. Intensive Care Med 2017; Azoulay et al. JAMA 2018). Furthermore, we assume that randomization will balance the proportion of patients with remitting hematological malignancy in both groups.

2. Randomization up to 6 hours from inclusion may delay treatment in whatever form and may affect outcome. need to be shortened in my opinion.
Answer: It is true that delayed NIV initiation was associated with increased rate of failure and mortality. However, the purpose of this criterion is precisely to avoid the late inclusion of patients with respiratory failure. It is important to note that the use of NIV or HFOT before randomisation was allowed. Moreover, for patients treated with standard oxygen therapy before randomisation, 2 trials did not report any difference between HFOT and standard oxygen therapy or between NIV and standard oxygen therapy. Therefore, we believe that this maximal 6-hour window prior the start of the allocated oxygenation strategy is not harmful. The purpose of this 6-hour time frame has been added in the Intervention section.

3. Set clinical criteria to define improvement after initiation of NIV in HFOT with NIV arm.
Answer: The clinical improvement after NIV initiation will be assessed by the attending physician. Indeed, there are various ways to define improvement in patients treated with NIV (vital signs,

subjective feeling, dyspnea, assessment by the attending physician, nurse or respiratory therapist). The aim of this improvement criteria was to prompt physicians to continue NIV if the patient has not improved after 4 hours of NIV. The approach to assess improvement under NIV has been added in the Control group section.

4. Evaluate the etiology of ARF on outcomes.
Answer: Thank you very much for this suggestion. A subgroup analysis will be performed according to the cause of ARF will be performed. A paragraph has been added in the Predetermined Subgroup Analysis section.

Reviewer: 4
Reviewer Name: Laveena Munshi
Institution and Country:
Interdepartmental Division of Critical Care Medicine
University of Toronto
Canada
Please state any competing interests or state 'None declared': None

RESEARCH QUESTION/OBJECTIVES:
This is an important and timely question. It focuses on a more "severe" cohort of acute hypoxemic respiratory failure within immunocompromised patients.
It addresses many physicians concerns about the historic evidence suggesting benefit of NIV which are based upon 2 outdated RCTs for which the approach to acute respiratory failure with (diagnosis and management) has evolved. As the authors outline, there has been observational data across the immunocompromised and non-immunocompromised subgroups that show that NIV failure is associated with an increased mortality.

1. In the secondary analysis of Lung Safe focused on immunocompromised patients, NIV was used as first line in approximately 21% of patients with ARDS – which highlights the importance of achieving greater clarify on this subject. My only suggestion would be to consider reporting this high frequency of NIV use across this population (Cortegiani et al ICM 2018).
Answer: Thank you for your comment. The frequent use of NIV as a first-line treatment in this clinical setting has been added in the Introduction section.

I understand that this study is nearly complete based upon their timeline outlined therefore this review is limited to reviewing the rationale and clarity of the methodology
ABSTRACT:
The abstract presents a balanced overview of the issues.
DESIGN:
POPULATION:
Pragmatically many physicians institute HFNC or NIV when patients are failing continuous oxygen therapy. INVICTUS and the HIGH trial demonstrated that NIV vs. continuous oxygen therapy (COT) and HFNC vs COT do not reduce intubation rates/mortality. However, the inclusion criteria of saturation <90 or paO2 <60 on room air may not reflect the use of these non-invasive currently. The inclusion criteria in the design of this study represents a "more severe" subset of early hypoxemic respiratory failure compared to the previous trials (P/F <300 on 10L/min)
This study is novel in that its focused on the immunocompromised population
Exclusion criteria are appropriate.
INTERVENTION/COMPARATOR:
The authors have protocolized the study intervention and comparator.

Through their design they attempt to address one of the previous theories for harm associated with NIV application (injurious ventilation) through their more rigorous protocol focusing on (1) a more protective ventilatory approach, and (2) minimizing interruption of alveolar recruitment through alternating NIV with HFNC
It is novel that the authors propose a criterion for weaning after 48 hours of exposure

A few questions for consideration/clarity
2. It would be useful for the authors to include their titration of FIO2 in the HFNC group. Is there a threshold of FiO2 where they drop the flow? How do they approach patients who cannot tolerate flows of 60L/min?
Answer: Thank you for this comment. Within the first 48 hours after randomisation, FiO2 will be set as low as possible to obtain a SpO2 ≥ 92% with a flow maintained at 60 L/min during this time frame. Then, flow will be decreased at the attending physician discretion and FiO2 will be set to obtain a SpO2 ≥ 92%. For patients experiencing HFOT intolerance at 60 L/min despite reinsurance, flow will be decreased to the highest level tolerated. This has been added in the Interventional group section. Moreover, as suggested below, a post-hoc analysis will be performed in patients without protocol deviation.

3. I do not see a protocol outlined on the approach to managing NIV. My presumption is that if the tidal volumes are greater than 8cc/kg they will just reduce the driving pressure. If they continue to be high – will they just maintain CPAP through NIV?
Answer: Thank you for this comment. For patients experiencing expired tidal volumes greater than 8 mL/kg of predicted body weight, we proposed to decrease the level of pressure support up to 5 cmH2O, but not CPAP. The complete list of settings adjustments has been added in the Control group section. Moreover, as you suggested below, a post-hoc analysis will be performed in patients without protocol deviation.

OUTCOME:
Primary and secondary outcomes are appropriate

ANALYSIS/METHODS:
Methods described clearly, thoroughly and appropriate. I have no major concerns as the statistical approach is sound

4. I have a few minor inquiries outlined below. While they will conduct an intention to treat analysis, is there a plan to also per protocol analysis?
Answer: You are right. We planned to do a per protocol analysis. A paragraph has been added to the Statistical methods section.

5. I think it would be important as there may be the risk of the following deviations and having clarity as to whether these deviations impact the utility would be important:
- Patients who are randomized to NIV+HFNC who do not tolerate 12 hours of NIV
- Patients who have tidal volumes that are outside of the lung protective protocol (although this is limited by the inability to measure tidal volumes in the HFNC group) but a comparison of those who achieved <8cc/kg via NIV against HFNC would be interesting
- Patients who may not tolerate 60L/min of flow through HFNC
- Patients who may cross over within the first 48 hours at the discretion of the physician
- Patients who, after the 48 hour time period, cross over into the alternative arm and have a sustained exposure to that arm (I am not sure the risk of this based upon the practice across these institutions)

Answer: You are right. The proportion of patients who could achieve the protocol without violation is unknown and it is of paramount importance to test the different subgroups you proposed. Hopefully,

the proportion of cross over will be limited. A paragraph has been added in the Predetermined Subgroup Analysis section.

Sample size calculation
Their projected 28-day mortality rates are 35% mortality in the NIV arm; and an anticipated 15% 28-day mortality benefit from HFNC are sufficiently justified in their protocol despite the differences across INVICTUS (lower NIV mortality – patients less severely ill) and HIGH (higher HFNC mortality – but a subset of these patients died before intubation). A 15% difference is a reasonable target and the same size appears feasible

6. A very minor point – what is the nutrition practice at these institutions with respect to nutrition on HFNC and NIV? Is it anticipated that most of these patients will remain NPO because of the concern about intubation? Or, do they allow HFNC pts to eat but not NIV? After a few hours if stable, will they allow HFNC to eat or continue NG tube feeds? Will that be the practice between breaks of NIV?
Answer: The point you raised is extremely important. Data about the nutrition practice in immunocompromised critically ill is scarce (Terzi et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study Crit Care 2017;21:293). In our study, nutrition practice was left at the attending physician discretion. However, we performed an ancillary study to describe the nutrition practice in patients included among participating centres who approved the amendment. From inclusion to day 28 or intubation or ICU discharge or death, the type of nutrition (enteral per os, enteral via a nasogastric tube, or parenteral), the amount of calories intake per day, the existence of complications related to nutrition and the reason for maintaining patients NPO. A paragraph has been added to the Statistical Methods section.
LIMITATIONS AND DISCUSSION:
Clear, no issues

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Lim Beng Leong<br>Ng Teng Fong Hospital<br>National University Hospital Cluster<br>Singapore |
| **REVIEW RETURNED** | 24-Apr-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | I thank the editor for allowing me to review the revised manuscript. The authors have added and emphasized the shortcomings of previous studies and highlighted why their study was urgently needed in the introduction.<br>I am satisfied with the rest of the responses for my comments. Of course, the lack of an interim analysis with stopping guidelines is a pity in such a multi-centre trial. |

| | |
|---|---|
| **REVIEWER** | Jun Duan<br>The First Affiliated Hospital of Chongqing Medical University, Chongqing, China |
| **REVIEW RETURNED** | 23-Apr-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | My concerns have been answered well. |

| | |
|---|---|
| **REVIEWER** | Bushra Mina<br>Lenox Hill Hospital<br>Northwell Health<br>Hofstra School of Medicine<br>New York, USA |

| | |
|---|---|
| **REVIEW RETURNED** | 21-Jul-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | the study has a clinical implication and is addressing an essential topic in treating de novo ARF. It will guide physicians in treating patients with HFNO vs NIV and the role of HFNO with NIV |

| | |
|---|---|
| **REVIEWER** | Laveena Munshi<br>University of Toronto, Canada |
| **REVIEW RETURNED** | 17-Apr-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | I have no further concerns or questions. I look forward to reading the results of this study. |