Author's response to reviews

Title: Early Noninvasive Ventilation for Acute Respiratory Failure in Immunocompromized Patients: Study protocol for a multicenter Randomized Controlled Trial (IVNlctus)

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Author's response to reviews: see over
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Dear editor,

Please find enclosed the revised version of the Manuscript MS: 1970690465126461 entitled "Early Noninvasive Ventilation for Acute Respiratory Failure in Immunocompromized Patients: Study protocol for a multicenter randomized Controlled Trial (IVNIctus)"

We would like to thank you and the Reviewers for their help in considerably improving our manuscript.

All the comments and suggestions have been taken into account and a point-by-point reply is provided in a separate file, with pertinent sentences or word fragments clearly mentioned.

We have uploaded a "Marked up" version of our previous manuscript, a clean version of the revised manuscript, and a detailed point-by-point response to reviewer comments.

We hope this version will be found suitable for publication in Trials journal. As the corresponding author, I remain at your entire disposal for any further indications.

Sincerely,

Virginie Lemiale, MD,
a) For a correct data collection the FiO₂ should be measured. Indeed especially for those patients who will breath through a venturi mask with an high peak flow, the FiO₂ delivered through the system might be simply “nominal”. Consequently in order to be sure of having comparable data the FiO₂ should be reliably determined and in the present design this is not taken into consideration.

We agree with the reviewer and FiO2 would be collected in both group and most of centers use venturi mask with a good estimation of FiO2. For the patients who will receive oxygen through non venturi mask, assessment of FiO2 will be performed according oxygen delivery system and oxygen flow following the data used in EPIC II study [Vincent JL JAMA. 2009; 302(21):2323-9].

This sentence had been added p 14/24 : “For patients receiving oxygen through mask, FIO2 will be estimated according oxygen delivery system and oxygen flow.”

b) As patients will receive both HFOT and low flow O2 therapy (< 9 l/min) how will you manage the stratification of the population? Looking at the different characteristic of the delivering systems and effects, the randomization should imply a three arms. The present design is unclear on this aspect.

Thank you, we added sentence in the manuscript. All patients included in the study will receive oxygen through venturi mask or through nasal canula. None of them will receive oxygen through humidified high flow oxygen canula (HFNC) system before randomization. After randomization, patients will be able to receive humidified High flow cannula. We performed stratification with only two arms according to the severity of acute respiratory failure based only on oxygen need. HFNC use will be recorded in the data and secondarily analyzed.

This sentence had been added p 13/24 : Before randomization, none of patient will receive humidified high flow oxygenation. Severity of acute respiratory failure will be only assessed with the oxygen flow need at randomization, though venturi mask or nasal cannula. After randomization, patient will receive humidified high flow cannula according physician. Humidified high flow cannula use will be recorded and analyzed.

c) What early NIV really means should be better clarified.

Early NIV is defined as NIV treatment for patients with acute respiratory failure without any other organ failure or intubation criteria (intubation criteria would be described further).

Editorial requests:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?__________ : study protocol for a randomized controlled trial.?
Title had been changed

2. Please include a statement in your Methods section explaining that you obtained informed consent from each participant. *This statement had been added to the method section (ethic paragraph)*

3. Please include a competing interests section at the end of the manuscript, before the reference list. If the authors have no competing interests, please state: "The authors declare that they have no competing interests."
   *This statement had been added.*