

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	WHO O2CoV2: Oxygen requirements and respiratory support in patients with COVID-19 in low- and middle-income countries – protocol for a multi-country, prospective, observational cohort study
AUTHORS	Relan, Pryanka; Murthy, Srinivas; Marshall, John; Annane, Djillali; Chevret, Sylvie; Arabi, Yaseen; Waweru-Siika, Wangari; Dominguez Rodriguez, Sara; Convocar, Pauline; Diaz, Janet; Respiratory Support Research Group, World Health Organization; O2CoV2 International Study Steering Committee, World Health Organization

VERSION 1 – REVIEW

REVIEWER	Guo, Qiang First Affiliated Hospital of Soochow University, Critical Care
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	<p>Thank you for giving me the possibility to review the protocol by Pryanka Relan and coauthors. When reading the manuscript, I have the following remarks:</p> <ol style="list-style-type: none">1. This subject is meaningful. In the age of high-tech medicine, life-support technologies and equipment are essential, but not everyone has access to them, especially patients in low- and middle-income areas. This research protocol focused on the oxygen requirements and respiratory support of COVID-19 patients in low- and middle-income countries, which are necessary to understand and improve the relatively weak health infrastructure and healthcare.2. On Page 20 PAST MEDICAL HISTORY, mental illness may need to be covered.3. On Page 22 10 c, the number of receiving COVID-19 vaccinations and the time of the last vaccination may also be important.4. Fig 1. The Multistate model shows a one-way transition of the disease state, but in clinical practice, the condition will not only worsen but also improve. Therefore, transitions, for example, from IMV to NIV or standard oxygen therapy may also be covered.5. Table 1. The analysis of BMI should not only include obese people, but also lean people.6. Although this protocol is very interesting, its feasibility is still worrying. First of all, three years have passed since the outbreak of COVID-19, and the current morbidity and mortality are different from those at the beginning of the epidemic. On January 20, 2023, the number of people currently hospitalized was only 286 (https://news.google.com/covid19/map?hl=en-US&mid=%2Fm%2F05kj_&gl=US&ceid=US%3Aen), which may pose difficulties with sample size for prospective studies. Secondly, with the change in concepts and policies, the clinical diagnosis and treatment of COVID-19 have changed. Compared with previous years, testing for SARS-COV-2 has decreased, and most of them were given symptomatic treatment including cooling, anti-infection,
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	and respiratory support Whether diagnosed with COVID-19 or not, and the "confirmed" cases decreased accordingly.
REVIEWER	Ore, Timothy Commission for Hospital Improvement, Department of Health
REVIEW RETURNED	19-Apr-2023
GENERAL COMMENTS	A well written study protocol on an important area, with a highly probability of filling existing gaps in knowledge and even extending knowledge. For instance, a 2020 review (Zelansko J et al, Neonatal oxygen therapy in low-middle income countries, Journal of Global Health Reports, Vol 4, April) found that there is a lack of data that provides direct estimates of availability of neonatal oxygen equipment and related clinical applications of oxygen therapy across health systems, particularly around the usage and availability of necessary monitoring equipment. That review inferred that attention to the maintenance of oxygen and ancillary equipment for neonates and quality improvement initiatives to promote adherence to those guidelines can reduce the morbidity and mortality burden among neonates in low and lower-income countries. And a World Health Organisation report (25 February 2021) has estimated that over half a million Covid-19 patients in low-middle income countries need oxygen treatment daily. The statistical analysis methods proposed by the study protocol is also impressive.

VERSION 1 – AUTHOR’S RESPONSE

Reviewer 2 comments:

Thank you for your review. We saw no comments to address.

Reviewer 1 comments:

1. This subject is meaningful. In the age of high-tech medicine, life-support technologies and equipment are essential, but not everyone has access to them, especially patients in low- and middle-income areas. This research protocol focused on the oxygen requirements and respiratory support of COVID-19 patients in low- and middle-income countries, which are necessary to understand and improve the relatively weak health infrastructure and healthcare.

Thank you for your kind comment.

2. On Page 20 PAST MEDICAL HISTORY, mental illness may need to be covered.

Thank you for this comment. We have added mental illness into the CRF for this publication. However we do note it may be infeasible to obtain this information for sites who have already collected data.

We did consider and discuss this item’s inclusion in developing the list of concurrent illnesses. We used what was suggested to be a risk factor for severe/critical COVID-19. As such “Dementia” was suggested by the WHO HQ Brain Health Unit, with option to allow inclusion of other mental illnesses as “other”.

3. On Page 22 10 c, the number of receiving COVID-19 vaccinations and the time of the last vaccination may also be important.

Thank you for this comment. We share the understanding that this may be useful for descriptive information. We have added 2 new questions into the CRF for this publication. However we do note it may be infeasible to obtain this information for sites who have already collected data.

4. Fig 1. The Multistate model shows a one-way transition of the disease state, but in clinical practice, the condition will not only worsen but also improve. Therefore, transitions, for example, from IMV to NIV or standard oxygen therapy may also covered

Thank you for raising this important point. This issue was discussed at length by the Study Steering Committee. Our decision to focus on escalating transitions of severity is primarily based on their clinical relevance. The progression of COVID-19 often follows a path of escalating severity before improvement, and understanding these transitions can provide key insights into disease progression and patient outcomes.

Moreover, we have chosen this approach to limit the risk of multiple testing and consequently reduce the potential for false positives. By focusing our analysis on a more streamlined and realistic pathway of disease progression, we can enhance the robustness of our results and provide more reliable conclusions.

Additionally, including all transitions, both escalating and de-escalating, in our model would significantly increase the complexity of the analysis. This would necessitate a substantially larger sample size to ensure adequate power for detecting statistically significant effects. As such, our focus on transitions of escalating severity is a pragmatic decision to ensure our study is feasible and statistically sound with the available data.

5. Table 1. The analysis of BMI should not only include obese people, but also lean people.

Thank you for this comment. We have made the suggested change.

6. Although this protocol is very interesting, its feasibility is still worrying. First of all, three years have passed since the outbreak of COVID-19, and the current morbidity and mortality are different from those at the beginning of the epidemic. On January 20, 2023, the number of people current hospitalized was only 286 (https://news.google.com/covid19/map?hl=en-US&mid=%2Fm%2F05kj_&gl=US&ceid=US%3Aen), which may pose difficulties with sample size for prospective studies. Secondly, with the change in concepts and policies, the clinical diagnosis and treatment of COVID-19 have changed. Compared with previous years, testing for SARS-COV-2 has decreased, and most of them were given symptomatic treatment including cooling, anti-infection, and respiratory support Whether diagnosed with COVID-19 or not, and the "confirmed" cases decreased accordingly.”.

Thank you for this comment. We have now addressed this in the Strengths and Limitations section.

Indeed the implementation of this study at different phases of the pandemic will result in various findings. However, we were very careful to include in the inclusion criteria, all those who are “suspected” to have COVID-19, which encourages enrolment of patients at the very early part of their admission to an emergency unit or similar prior to COVID-19 diagnosis. This then also allows for possible extrapolation of findings to all who meet other inclusion criteria and importantly those who require oxygen. Already, 23 countries have begun implementation of the study and many others may be able to adapt some inclusion criteria regarding the COVID-19 diagnosis.