

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Design and rationale of the COVID-19 Critical Care Consortium, international, multicenter, observational study: A study protocol
<b>AUTHORS</b>	Li Bassi, Gianluigi; Suen, Jacky; Barnett, Adrian; Corley, Amanda; Millar, Jonathan; Fanning, Jonathon; Lye, India; Colombo, Sebastiano; Wildi, Karin; Livingstone, Samantha; Abbate, Gabriella; Hinton, Samuel; Liquet, Benoit; Shrapnel, Sally; Dalton, Heidi; Fraser, John

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Lowell Ling The Chinese University of Hong Kong, Hong Kong, China
<b>REVIEW RETURNED</b>	28-Jun-2020

<b>GENERAL COMMENTS</b>	<p>This is an ambitious study which hopes to collect multinational observational data on patients with COVID-19 who are admitted to the ICU. Data is clearly important to overcome this pandemic and the authors should be commended for achieving participation across many ICUs and countries in this study. However there are major concerns including:</p> <ol style="list-style-type: none"><li>1. Inclusion criteria needs to be clarified: will patients who are SARS-CoV-2 positive but came to the ICU for other reasons be included?</li><li>2. Please clarify if this is retrospective or prospective. In the study title it is stated as prospective, but the research protocol it is prospective/retrospective. This has major implication for data integrity and strength of the study. From the included figure it seems the data prior to ICU will be retrospective and after ICU admission it will be prospective.</li><li>3. Please clarify what the criteria for suspected COVID-19 will be. This is particularly important since many under resourced settings may not have testing capabilities.</li><li>4. Please clarify if patients will be followed up until death or discharge. Parts of the manuscript says that patients will be followed up until death but other parts including the protocol says until 28 days after ICU or hospital discharge. So if a patient survives beyond 28 days after ICU data will still be collected until hospital discharge or death? Also please note the recently published recommendation from "WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection" is for 60 days follow up or hospital discharge.</li><li>5. The authors state that potential heterogeneity is mitigated by the international composition of the consortium. Data will be collected from different ICUs from different countries with different</li></ol>
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	<p>healthcare systems. However there needs to be data on the healthcare system, country burden and performance characteristics of the participating ICUs. It is not clear if this data will be collected to interpret the expected heterogeneity between study sites. Please consider collecting data on individual ICUs including organization factors such as nurse and doctor to patient ratio, capacity, expanded capacity.</p> <p>6. Use of specific invasive interventions such as mechanical ventilation or ECMO may be limited by resources, staffing and patient load during extreme case loads, even in normally well resourced settings. This study needs to address how these limitations will be accounted for otherwise the data on when mechanical ventilation was used or differences in mortality may not be easily interpretable. The potential of this study should be to tease out these differences across healthcare settings/regional burden of COVID and without data from point 5 it is not clear how this study will differentiate itself from existing published large cohorts of COVID patients from different countries.</p> <p>7. The main study aims (for the initial primary study) seems to be to "describe clinical features; severity of pulmonary dysfunction; incidence of ICU admission and use of mechanical ventilation, coagulatory and thrombotic derangement, and ECMO technical characteristics; duration of ECMO complications and survival of patients with COVID-19." However apart from the ECMO data, multiple large studies have already provided information on the clinical features, incidence of ICU admission and details of mechanical ventilation. It is not clear how this study adds novel information. Furthermore, these are all data that are already included in the WHO/ISARIC database. Therefore the characteristics of this study is best akin to a registry on critically ill patients with COVID rather than a purpose driven prospective trial. If the goal was to study ECMO use in COVID-19, then it would be best to narrow the cohort to just ECMO patients.</p> <p>8. In general the aim of collecting lots of data on critically ill patients with COVID may help dissect out essential information about characteristics and management of these patients. However collecting lots of data does not equate to good detailed data for specific endpoints in mind, in particular:</p> <p>--although data on prone ventilation is collected, it is only yes or no each day rather than duration this may affect interpretation since it is longer proning per session that is key to success according to ARDSNet trial, this data is contained in the Core Critical Care Module (Part B) of ISARIC CRF, but it is not clear if this study will make it mandatory to collect this data</p> <p>--use of recruitment maneuver is documented but it is not clear how it is performed, and the way it is performed may affect need for proning/neuromuscular blockade or ECMO</p> <p>--more explanation is needed to address data integrity and quality, particularly during this pandemic when resources are already stretched to ensure fidelity of data</p>
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<b>REVIEWER</b>	Jordi Rello CIBERES, Instituto de Salud Carlos III, Spain
<b>REVIEW RETURNED</b>	22-Aug-2020

<b>GENERAL COMMENTS</b>	This is an important collaborative study and the protocol is well designed. Regarding outcomes, progression of disease should incorporate the 7 levels reported by the WHO. Mortality rate above 60%, as reported in the introduction, is due to suboptimal standard of care of intubated patients or limited resources. Much lower 28-day mortality has been reported in western countries and the figure should be edited. Mortality rate has a broad range depending of the surge. I suggest to enclose the prevalence in the region when a case report is filled, to have a dynamic picture. Lung compliance at intubation should be filled, and also initial ventilatory parameters.
<b>REVIEWER</b>	Mei Fong Liew National University Health System (NUHS) Singapore
<b>REVIEW RETURNED</b>	02-Sep-2020
<b>GENERAL COMMENTS</b>	Detailed study protocol and study parameters. Well thought through.

### VERSION 1 – AUTHOR RESPONSE

#### Response to the Reviewers:

##### Reviewer: 1

##### Reviewer Name: Lowell Ling

Institution and Country: The Chinese University of Hong Kong, Hong Kong, China

Please state any competing interests or state 'None declared': None declared.

This is an ambitious study which hopes to collect multinational observational data on patients with COVID-19 who are admitted to the ICU. Data is clearly important to overcome this pandemic and the authors should be commended for achieving participation across many ICUs and countries in this study. We thank Prof Ling for the affirmation of the importance of the study from the reviewer.

However there are major concerns including:

1. Inclusion criteria needs to be clarified: will patients who are SARS-CoV-2 positive but came to the ICU for other reasons be included?

Thank you for the reviewer's comment. In the methods section. we have updated the exclusion criteria to make clear that patients who are admitted to ICU for other concomitant causes will be excluded. As for the specific population of patients who were recently diagnosed with SARS-CoV-2 Infection and later admitted to the ICU for reasons not specifically related to the infection, we added the following line: *"In addition, patients who were recently diagnosed with SARS-CoV-2 infection and later admitted to the ICU for reasons not related to the SARS-CoV-2 infection will be excluded."*

2. Please clarify if this is retrospective or prospective. In the study title it is stated as prospective, but the research protocol it is prospective/retrospective. This has major implication for data integrity and strength of the study. From the included figure it seems the data prior to ICU will be retrospective and after ICU admission it will be prospective.

As a pragmatic study conducted during a time of great pressure on hospitals, the study has been designed to accommodate both prospective and retrospective data collection, depending on the site's capacity to collect data. To provide clarity for the reader, we have removed the word 'prospective' from the title and abstract methods. We have also added a sentence to the manuscript under "Data Collection Methods" – "Data can be collected and entered prospectively (preferred) or retrospectively dependent on the participating site's resources."

3. Please clarify what the criteria for suspected COVID-19 will be. This is particularly important since many under resourced settings may not have testing capabilities.

Thank you for the comment. As rightly pointed out by the reviewers, we have decided against having a set of strict definition for suspected COVID-19, due to variation in resources and settings among collaborating institutions across the world and decided that the criteria for suspected COVID-19 will be determined by the attending physician. We have added a sentence to the manuscript under " Study Eligibility".

4. Please clarify if patients will be followed up until death or discharge. Parts of the manuscript says that patients will be followed up until death but other parts including the protocol says until 28 days after ICU or hospital discharge. So if a patient survives beyond 28 days after ICU data will still be collected until hospital discharge or death?

Patients will be followed up until death, or discharge, or up to 28 days after ICU admission, whichever occur last. Therefore, if a patient survives ICU and remains in a hospital setting beyond 28 days after ICU admission, follow up would cease at hospital discharge. If a patient survives after ICU and is discharged from the hospital earlier than 28 days post ICU admission, the data collection will cease upon discharge but patients will still be followed up to 28 days to assess survival.

Also please note the recently published recommendation from "WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection" is for 60 days follow up or hospital discharge.

We thank the reviewer on raising the issue of the recent published recommendation. Unfortunately, due to the lack of funding/resources, as well as a large part of our consortium is low-middle income countries, we believe that the current follow-up period as per the above criteria is the maximum duration which most of our members can reliably achieved at this point. Nevertheless, to provide valuable data

in accordance with WHO requirements, in all our analysis we are aiming to compute outcomes from multistate model analysis up to 60 days from intensive care unit admission and develop probability plots for the model states of not mechanically ventilated, on mechanical ventilation, discharge from ICU and death.

5. The authors state that potential heterogeneity is mitigated by the international composition of the consortium. Data will be collected from different ICUs from different countries with different healthcare systems. However there needs to be data on the healthcare system, country burden and performance characteristics of the participating ICUs. It is not clear if this data will be collected to interpret the expected heterogeneity between study sites. Please consider collecting data on individual ICUs including organization factors such as nurse and doctor to patient ratio, capacity, expanded capacity.

We thank the reviewer for their insight on this issue and agree that these further analyses would have been of great interest. The intent of the current study is to provide clinicians at the bedside data on disease characteristics, progression, treatment and outcomes in as close to real-time as possible. Thankful to the reviewer's suggestion we are discussing internally between data management team and chief investigators changes to the electronic CRF to characterize further ICU where patients are enrolled. We added the following paragraph in the discussion:

*"This potential heterogeneity is mitigated by the international composition of the consortium. In addition, we are planning to further characterize individual ICUs, collecting data on nurse/doctor to patient ratio, capacity, and potential expanded capacity."*

6. Use of specific invasive interventions such as mechanical ventilation or ECMO may be limited by resources, staffing and patient load during extreme case loads, even in normally well resourced settings. This study needs to address how these limitations will be accounted for otherwise the data on when mechanical ventilation was used or differences in mortality may not be easily interpretable. The potential of this study should be to tease out these differences across healthcare settings/regional burden of COVID and without data from point 5 it is not clear how this study will differentiate itself from existing published large cohorts of COVID patients from different countries.

We thank the reviewer for the suggestion. As mentioned in the previous point, the objective of the consortium is to better characterise the best practice in supporting critical COVID-19 patients. Yet, we fully agree with the reviewer that case loads, resources limitations and other social, economic and political factors can all impact on patient outcome. Thus, we are planning to marginally revisit the electronic case report form to gather information on these important points.

7. The main study aims (for the initial primary study) seems to be to "describe clinical features; severity of pulmonary dysfunction; incidence of ICU admission and use of mechanical ventilation, coagulatory and thrombotic derangement, and ECMO technical characteristics; duration of ECMO complications and survival of patients with COVID-19." However apart from the ECMO data, multiple large studies

have already provided information on the clinical features, incidence of ICU admission and details of mechanical ventilation. It is not clear how this study adds novel information. Furthermore, these are all data that are already included in the WHO/ISARIC database. Therefore the characteristics of this study is best akin to a registry on critically ill patients with COVID rather than a purpose driven prospective trial. If the goal was to study ECMO use in COVID-19, then it would be best to narrow the cohort to just ECMO patients.

We appreciate that there have been a lot of national registries and databases published on COVID-19 patients. However, as far as the authors are aware, we are the only international data base focus exclusively on ICU patients with a true global input. We believe there is a strong merit for our study as there are increasing evidence to show that people of different countries/geographical region/race/ethnicity responded to COVID-19 differently and may require different management and support in the ICU. This is yet to be addressed by any other database or studies.

With regards to WHO/ISARIC database, we continue to work closely with the ISARIC team, and have done so since January 2020. We would like to point out that both the ISARIC team and our consortium has representatives at each other's steering committee. As mentioned above, it is a collective decision with key members of the ISARIC team that there is no overlap of our efforts. Of note, the vast majority of large databases of COVID-19 patients available fully describe hospitalized patients, but without specific focus on ICU patients. Our study is targeted towards an in-depth examination of critical care for COVID-19 patients in ICU in order to identify the best practice and patient management. In contrast, the ISARIC database and many others focus largely on broad, epidemiological data and is much more suitable to address broader, public health questions raised by the reviewer previously.

8. In general the aim of collecting lots of data on critically ill patients with COVID may help dissect out essential information about characteristics and management of these patients. However collecting lots of data does not equate to good detailed data for specific endpoints in mind, in particular:

--although data on prone ventilation is collected, it is only yes or no each day rather than duration this may affect interpretation since it is longer proning per session that is key to success according to ARDSNet trial, this data is contained in the Core Critical Care Module (Part B) of ISARIC CRF, but it is not clear if this study will make it mandatory to collect this data  
--use of recruitment maneuver is documented but it is not clear how it is performed, and the way it is performed may affect need for proning/neuromuscular blockade or ECMO  
--more explanation is needed to address data integrity and quality, particularly during this pandemic when resources are already stretched to ensure fidelity of data

We acknowledge that a more detailed data would have been useful however, as a pragmatic trial conducted during a pandemic, the investigators were very mindful that overburdening sites with data collection would jeopardise the ability of the study to collect any data at all. Therefore we elected to keep the case report form as minimal as possible and collected only critical data from the ICU stay.

We also understand that each site will have differences in how they deliver interventions (eg, recruitment manoeuvres) however the study is not aimed at this level of interrogation of clinical practice. Nevertheless, the COVID-19 Critical Care Consortium has already created various subgroups to inclusively investigate neurological, cardiac and renal effects of SARS-CoV-2. This further corroborates potentials of the network to further expand on the analysis of patients as suggested by the reviewer. Finally, in the future, we hope that we can use the network created by the Consortium to provide more in-depth analysis of how interventions were delivered or any and their effects of patient outcome. Once again, we thank the reviewer for the very thorough and detailed comments.

**Reviewer: 2**

Reviewer Name: Jordi Rello

Institution and Country: CIBERES, Instituto de Salud Carlos III, Spain

Please state any competing interests or state 'None declared': none declared

This is an important collaborative study and the protocol is well designed.

We deeply thank Prof. Rello for reviewing our manuscript and for his insightful suggestions

Regarding outcomes, progression of disease should incorporate the 7 levels reported by the WHO.

We thank you for this important comment. We would like to emphasize that one of the strengths of our observational study is the strong association between the ISARIC and the COVID-19 CCC case report forms. The main reason for originally linking our CRF to the ISARIC one was that ISARIC had developed the CRF under close scrutiny by the WHO and in accordance to all WHO requirements for describing infectious diseases and outcomes, including disease progression. Thus, for each of the patients enrolled into the COVID-19 CCC we are able to fully access the ISARIC sections and describe disease progression and outcomes as suggested by the WHO.

Mortality rate above 60%, as reported in the introduction, is due to suboptimal standard of care of intubated patients or limited resources. Much lower 28-day mortality has been reported in western countries and the figure should be edited. Mortality rate has a broad range depending of the surge. I suggest to enclose the prevalence in the region when a case report is filled, to have a dynamic picture.

Thank you for the suggestion to update the mortality figures – this has been attended in the manuscript introduction.

Lung compliance at intubation should be filled, and also initial ventilatory parameters.

In terms of changing the CRF to collect lung compliance and ventilatory parameters at intubation, the reviewer's suggestion is entirely valid however the investigators had to choose the most critical data

points to collect in this pragmatic study during this pandemic. Lung compliance would require the use of a transesophageal catheter and expertise that cannot be broadly expected from the large network of collaborators of our network. Yet, regional prevalence will certainly be added to subsequent manuscripts, particularly those which focus on the impact on COVID on sites' capacity to respond to the pandemic and its effect on patient outcomes.

**Reviewer: 3**

Reviewer Name: Mei Fong Liew

Institution and Country:

National University Health System (NUHS)

Singapore

Detailed study protocol and study parameters. Well thought through. We are grateful for the support of the reviewer and for her time reviewing our manuscript.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Lowell Ling The Chinese University of Hong Kong, Hong Kong, China
<b>REVIEW RETURNED</b>	04-Nov-2020

<b>GENERAL COMMENTS</b>	Thank you for addressing my concerns. This is an important and timely collaborative study. The plan for open access is particularly helpful for subsequent hypothesis generating research.  My only suggestion is: In relation to my previous point #2: regarding retrospective and prospective, thank you for clarifying that recruitment will be mixed depending on study sites. Please clarify page 6 line 31 as it still has prospective in the study design.
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<b>REVIEWER</b>	Jordi Rello Vall d'Hebron Institute of Research, Barcelona, Spain
<b>REVIEW RETURNED</b>	05-Nov-2020

<b>GENERAL COMMENTS</b>	The manuscript has been improved replying to reviewers' queries.
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