

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Study protocol: The Philippine COVID-19 Outcomes: a Retrospective study Of Neurological manifestations and Associated symptoms (The Philippine CORONA Study)
<b>AUTHORS</b>	Espiritu, Adrian; Sy, Marie Charmaine; Anlacan, Veeda Michelle; Jamora, Roland Dominic

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Bo Hu Huazhong University of Science and technology, China
<b>REVIEW RETURNED</b>	09-Jul-2020

<b>GENERAL COMMENTS</b>	<ul style="list-style-type: none"> <li>• What are the highlights of this study and how does it differ from the published research so far?</li> <li>• In the “Main outcomes considered” section, the definition of some outcomes should be quantificat evaluation, for example: the Respiratory failure tachypnea (What's the respiratory rate), abnormal blood gases (hypoxemia or hypercapnia), signs of increased work of breathing ( precise quantity interpretation), and requiring oxygen supplementation.</li> <li>• Both electrophysiologic studies and lumbar puncture are invasive, the author didn't describe the basis on which the patient needs these test and how to avoid cross infection.</li> </ul>
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<b>REVIEWER</b>	Rhys Thomas Newcastle University, UK
<b>REVIEW RETURNED</b>	25-Jul-2020

<b>GENERAL COMMENTS</b>	<p>Much has happened from submission to my review – and I know that I could have been quicker about this. Therefore ‘it appears..may be..’ in the abstract looks a little out of date now</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32593341/">https://pubmed.ncbi.nlm.nih.gov/32593341/</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32637987/">https://pubmed.ncbi.nlm.nih.gov/32637987/</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32430621/">https://pubmed.ncbi.nlm.nih.gov/32430621/</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32570113/">https://pubmed.ncbi.nlm.nih.gov/32570113/</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32437313/">https://pubmed.ncbi.nlm.nih.gov/32437313/</a></p> <p>And there are other examples too – including the French NEJM paper, these need to be acknowledged in the introduction, bottom of page 3 too</p>
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	<p>The strengths and limitations are fair</p> <p>I am a little concerned that the authors jump straight to looking at pathogenic mechanisms, speculating about ACE2 and invasive potential. There are not sufficient current data to conclude on this point yet and the data they will capture will not be able to address this question.</p> <p>When it comes to the potential of a study to identify causation v correlation this paper may be helpful  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7299654/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7299654/</a></p> <p>It may not be possible – but I would collect MRI, EEG, CSF (and PCR in CSF) data – including post-mortem data if available. (I see the variable come later, thanks)</p> <p>I would also encourage the authors to look at psychiatric and altered mental state features, if this is possible – such as psychosis. If these are not included, then you may want to exclude these cases from our control group</p> <p>Please can you comment on whether individual consent is needed for data to be collected, or stored in the Epi Info database. Do you have ethics to go back to the individuals to answer later questions? (OK, ethics comes later – thanks)</p> <p>Are you collecting data on obesity, ethnicity? Are you in touch with the global COVID initiative, run by Tom Solomon in the UK and others? If not your data would put you in a great position to contribute.</p> <p>Best of luck with this great endeavour - well done</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Professor Bo Hu

Institution and country: Huazhong University of Science and Technology, China

1. What are the highlights of this study and how does it differ from the published research so far?

-Authors' response: Thank you for this excellent question. We would like to underscore the features of our study compared to other studies, as follows:

- Our study is designed to include a relatively larger sample of patients (our computed sample size is 1,342) with COVID-19 and will be conducted in 37 institutions from all over the country. The nationwide pooling of information may permit more reliable estimates of important data to be collected in this study.
- Most published studies dealt with occurrences of neurological symptoms/signs of COVID-19. In our study, we intend to provide reliable descriptive estimates of the frequencies of neurological complications, which were mostly described previously as case reports or case series.
- We intend to describe the neurodiagnostic features of COVID-19 (e.g., imaging, CSF analysis, electrophysiological studies) which were sparsely reported in the literature.

• Our study is aiming to directly associate neurological manifestations with important clinical endpoints in COVID-19 like mortality, respiratory failure, duration of ventilator dependence, ICU admission, length of ICU stay, and length of hospital stay among patients with COVID-19 disease. Based on our literature review, these relationships have not been sufficiently investigated.

2. In the “Main outcomes considered” section, the definition of some outcomes should be quantified evaluation, for example: the Respiratory failure tachypnea (What's the respiratory rate), abnormal blood gases (hypoxemia or hypercapnia), signs of increased work of breathing ( precise quantity interpretation), and requiring oxygen supplementation.

-Authors' response: Thank you for this valuable input. We have now rectified this in our revised manuscript. Kindly see page 8 (please skip page 9) and continued in page 10, under “Main outcomes considered”, “Respiratory failure”.

3. Both electrophysiologic studies and lumbar puncture are invasive, the author didn't describe the basis on which the patient needs these test and how to avoid cross infection.

-Authors' response: We fully considered the invasiveness of these procedures to our patients. This major issue was one of the reasons why we have limited our study to a retrospective review of medical charts and official results to obtain data from these tests.

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Reviewer #2: Professor Rhys Thomas

Institution and country: Newcastle University, UK

1. Much has happened from submission to my review – and I know that I could have been quicker about this. Therefore ‘it appears..may be..’ in the abstract looks a little out of date now

-Authors' response: Thank you for your valuable inputs. We have now updated the abstract, removing phrases like “it appears” and “may be”. Kindly see page 1, Abstract, under “Introduction”.

2.

<https://pubmed.ncbi.nlm.nih.gov/32593341/>

<https://pubmed.ncbi.nlm.nih.gov/32637987/>

<https://pubmed.ncbi.nlm.nih.gov/32430621/>

<https://pubmed.ncbi.nlm.nih.gov/32570113/>

<https://pubmed.ncbi.nlm.nih.gov/32437313/>

And there are other examples too – including the French NEJM paper, these need to be acknowledged in the introduction, bottom of page 3 too

-Authors' response: We appreciate the provision of these important articles. We have now fully incorporated these references as suggested by our esteemed review. Kindly see page 3 (paragraph 2) continued to page 4.

3. The strengths and limitations are fair

-Authors' response: Thank you for this assessment.

4. I am a little concerned that the authors jump straight to looking at pathogenic mechanisms, speculating about ACE2 and invasive potential. There are not sufficient current data to conclude on this point yet and the data they will capture will not be able to address this question.

-Authors' response: Thank you for your valuable inputs. We have now considered this suggestion and removed the mentioned statements. Kindly see page 3, paragraph 1.

5. When it comes to the potential of a study to identify causation v correlation this paper may be helpful

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7299654/>

-Authors' response: We would like to thank our esteemed reviewer for this article. We intend to apply the concepts discussed in this article and share this information to our collaborators. Furthermore, we have now used this article as one of our references. Kindly see page 3, paragraph 2, sentence 5 (continued to page 4).

6. It may not be possible – but I would collect MRI, EEG, CSF (and PCR in CSF) data – including post-mortem data if available. (I see the variable come later, thanks)

-Authors' response: Yes, we intend to obtain MRI, CSF, and electrophysiological (e.g., EEG) data for this study.

7. I would also encourage the authors to look at psychiatric and altered mental state features, if this is possible – such as psychosis. If these are not included, then you may want to exclude these cases from our control group

-Authors' response: Thank you for this recommendation. The Steering Committee of the CORONA Study Group has substantially deliberated this previously but has decided to exclude psychiatric symptoms like psychosis for this study.

8. Please can you comment on whether individual consent is needed for data to be collected, or stored in the Epi Info database. Do you have ethics to go back to the individuals to answer later questions? (OK, ethics comes later – thanks)

-Authors' response: Yes, the ethical considerations of our study come later in our manuscript. Thank you very much.

9. Are you collecting data on obesity, ethnicity? Are you in touch with the global COVID initiative, run by Tom Solomon in the UK and others? If not your data would put you in a great position to contribute.

-Authors' response: Our study plans to obtain data on obesity and nationality/ethnicity. It will be an honor to contribute by sharing our data to help fight against the COVID-19 pandemic. In line with this, we would like to gently request for the e-mail address of Professor Tom Solomon. Thank you.

10. Best of luck with this great endeavour - well done

-Authors' response: Thank you very much for your kind comments and helpful recommendations.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Rhys Thomas Newcastle University
<b>REVIEW RETURNED</b>	19-Sep-2020

<b>GENERAL COMMENTS</b>	As mentioned - This is Prof Solomon's email - tsolomon@liverpool.ac.uk  Thanks for the opportunity to look again at this excellent protocol. It is of great importance and the authors have carefully considered all advice. I have no further comments
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