PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PIM-COVID study: protocol for a multi-centre, longitudinal study measuring the psychological impact of surviving an intensive care admission due to COVID-19 on patients in the United Kingdom
AUTHORS	Waite, Alicia; Johnston, Brian; Boyle, Andrew; Cherry, M. Gemma; Fisher, Peter; Brown, Stephen; Jones, Christina; Williams, Karen; Welters, Ingeborg

VERSION 1 – REVIEW

REVIEWER	Gedik, Tugce Emiroglu İstanbul Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, geriatric
REVIEW RETURNED	03-Mar-2023

GENERAL COMMENTS	I like your study protocol. The study protocol was clear and purposeful. Thank you for your contribution to the literature.

REVIEWER	Didriksen, Maria Copenhagen University Hospital, Clinical Immunology
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	This is a review of the protocol entitled “The Psychological IMpact of surviving an intensive care admission due to COronaVIrus Disease 2019 (COVID-19) on patients in the United Kingdom”. The planned study is relevant and fills a gap in literature. My initial thought was why are some letters in capital (P IM CO VI D) in the title? Maye it is to present a cohort/collaboration (when I get to the results section, I see that this collaboration is called PIM-COVID). However, the reader does not know this from reading the title, so I would suggest dropping the capital letters or potentially introducing the PIM-COVID name in the Abstract section. ABSTRACT: I am missing a statement presenting the objective of this study (it can be deduced from the text, but it needs to be explicitly stated) INTRODUCTION: Presents the issue clearly. I have minor comments. 1) I am confused about the reported proportions: to begin with the authors state that 23-38% of ICU patients with non-COVID ARDS have symptoms of depression, anxiety and PTSD lasting a median of 33-39 months. Subsequently, the authors say these symptoms persist in up to 34% of ICU survivors after one year following their admission. Maybe I am missing something, but to me this does not match, since the first statement would mean that 50% of patients experience their symptoms for longer than 33-39 months.

	2) I suggest moving the last paragraph “This will be the first … “ to the next section “Study aims and objectives” STUDY AIMS AND OBJECTIVES: Relevant aims which are clearly presented. METHODS AND ANALYSIS: minor comments. 1) Table 2: Please define EQ-5D-5L 2) Multiple cohorts design: Consider including adjusted point prevalence (sex/age/socioeconomic position/previous psychiatric diagnoses)

REVIEWER	Grabbe, Linda Emory University, School of Nursing
REVIEW RETURNED	02-Apr-2023

GENERAL COMMENTS	This is an important topic worthy of research. The approach is sound and the writing is succinct. More up to date references on mental health after Covid will help. Do you have hypotheses regarding your findings? What limitations might you expect? 'The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
—> Many thanks for your comments.

Reviewer 2
My initial thought was why are some letters in capital (P IM CO VI D) in the title? Maye it is to present a cohort/collaboration (when I get to the results section, I see that this collaboration is called PIM-COVID). However, the reader does not know this from reading the title, so I would suggest dropping the capital letters or potentially introducing the PIM-COVID name in the Abstract section.
—> The title has been adjusted.

ABSTRACT: I am missing a statement presenting the objective of this study (it can be deduced from the text, but it needs to be explicitly stated)
—> We have added the main objectives to the abstract.

INTRODUCTION:
1) I am confused about the reported proportions: to begin with the authors state that 23-38% of ICU patients with non-COVID ARDS have symptoms of depression, anxiety and PTSD lasting a median of 33-39 months. Subsequently, the authors say these symptoms persist in up to 34% of ICU survivors after one year following their admission. Maybe I am missing something, but to me this does not match, since the first statement would mean that 50% of patients experience their symptoms for longer than 33-39 months.
—> The first statement is regarding patients who have ARDS, whereas the second statement refers to ICU patients generally. We anticipate that the vast majority, if not all, patients admitted to intensive care in the UK who were treated for COVID-19 will have had severe ARDS. Mortality rates of patients with severe ARDS tend to be higher than those from non-ARDS ICU admission. As such, we assume that patients with ARDS are sicker than general ICU patients, and therefore may be more at risk of more psychological distress.

2) I suggest moving the last paragraph “This will be the first … “ to the next section “Study aims and objectives”
—> We have moved this paragraph, thank you.

METHODS AND ANALYSIS: minor comments.
1) Table 2: Please define EQ-5D-5L
—> A definition for EQ-5D-5L has been added to Table 2.

2) Multiple cohorts design: Consider including adjusted point prevalence (sex/age/socioeconomic position/previous psychiatric diagnoses)
—> We specified the use of unadjusted point prevalence estimates for two reasons. First, we are unclear as to the population to which we would be adjusting the estimates (e.g., would this be the general population, non-Covid discharges from ICU, all discharges from ICU). Second, there is little information available on most indicators to make adjustments. We are, of course, aware that our population may differ on characteristics such as age and sex from other populations, thus, we will provide a breakdown of point prevalence rates according to these variables and examine odds of these influencing caseness.

Reviewer: 3
- More up to date references on mental health after Covid will help.
—> More up to date references have been added. We anticipate that this study will be the largest UK study assessing psychological outcomes solely in critically ill patients who have been treated for COVID-19.

- Do you have hypotheses regarding your findings?
—>There are many unique features of COVID that make it challenging to make concise hypotheses: the international nature of the pandemic with constant reminders on the media about COVID, the variations in national and regional restrictions during different waves, differences in hospital-specific rules around family visiting, the protective effect of furloughed workers and working from home rules, the harmful and/or protective effects of social distancing and lockdowns, the regional variations in follow-up service provision. Because it is such a complex landscape, with so many possibilities for outcomes we have not offered hypotheses. We have however added two sub-studies during the study, to add to the data from the surveys - namely interviews to better understand the experience of ICU survivors after leaving ICU and the survey of follow-up services to assess geographical variations in provision of support for ICU patients when they leave the hospital.

- What limitations might you expect?
—>There are a number of potential limitations. Firstly, we expect that there will be a group of patients who do not want to engage in the study (who either decline to participate or provide consent but do not answer any questionnaires). The second limitation will be that this study was designed to be led and conducted at study sites by trainees/junior doctors (interns/residents) and other junior members of the ICU multi-disciplinary team from other professions, with the support of a senior ICU clinician (ICU consultant/research nurse/psychologist/etc.). The study is also supported by the National Institute for Health Research (NIHR) and is on their research portfolio, which implies that research nurses also contribute and run the study at some sites. We plan to discuss limitations after analysis of the data, so that we can show the number of patients who participated as compared to the number screened and comment on the structure of the study teams.

We have tried to mitigate for some limitations in the study design, by trying to make the surveys as accessible as possible (allowing participants to conduct their surveys online, by email or by post) and by making the data collection by study teams as concise and flexible time-wise as possible.

“Protocol to measure the psychological impact” will make the nature of the article clearer
—> The title has been adjusted.

- A brief explanation of relationship between benzos and mental health outcomes of ICU patients would be helpful. Or at least a reference e.g., Kok 2018
—> The Kok reference has been added, thank you.

- You make no mention of long Covid but articles on long-covid mention neuopsychiatric problems including depression and anxiety. How will you account for the presence of long Covid? Will you include vaccination status as a clinical variable?
—>When we designed the study, the term long-COVID did not exist and vaccines were not available. Long-COVID symptoms can certainly be explored in the interview sub-study and discussed together with the study results. We will analyse the data to explore if there is in fact a difference in rates of psychological distress as compared to those previously described in non-COVID ICU patient populations.

- Explain what the traineeship is, briefly. Are these MDs becoming intensivists, hospitalists, internal med MDs? Is there any interprofessional collaboration? I looked at the 1st author’s website and it looks like this is a group being trained to do research as well. How much trainee time is freed up to allow for the investigation? Other healthcare entities might be interested in how this is set up.
—> This study is the first study to be run by the TRIC Network. A brief explanation of what the TRIC network is has been added to the manuscript. Authors AW, BJ and AB are intensive care specialist trainees (residents) who sit on the TRIC network committee and contribute to it in their spare time. No research training is offered through the TRIC network, other than the study-specific site initiation visits. The TRIC network is not restricted to doctors, but is for all ICM-interested clinicians to participate, representing the MDT nature of our teams. The study was designed for other trainees (interns/residents) and ICM-affiliated clinicians to be PIs and study team members, fitting in study involvement around clinical duties in a flexible manner.
We feel it would be better to describe who took part in the study when presenting the findings of the survey of study team members. We also think that our approach to designing the study in a flexible, ‘trainee-friendly’ manner would be better explored in a separate manuscript.

- Reduce spacing of lines: Survived to intensive care / high dependency unit discharge following an admission of ≥24 hours. It was confusing
—> This has been addressed, thank you.

- How are you using the HADS vs or with the anxiety and depression elements of the EQ?
—>The HADS will be used when reporting rates of anxiety and depression because it is more objective than the anxiety/depression element in EQ-5D-5L. The intention for including EQ-5D-5L was predominantly for a short subjective assessment of the physical symptoms patients experience. However, we plan to report all elements of EQ-5D-5L including the single-question self-assessment about whether participants feel anxious or depressed.

- For Table 2: A description of the APACHE score would be helpful; specify that physical and mental comorbidities are prior to ICU admissions; not clear if you are using the EQ depression and anxiety measures; clarify that Trauma refers to psychological trauma symptoms The category of Physical Data is misleading. Is Functional Data more accurate?
—> The following changes have been made to table 2:
-An explanation of APACHE has been added
-We have specified that physical and mental health comorbidities are pre-admission.

-‘Physical Data’ has been changed to ‘Functional Data’
-‘Trauma symptoms’ has been changed to ‘Psychological trauma symptoms’
We will be reporting all elements of EQ-5D-5L and have listed the EQ-5D-5L under Psychological and Functional Data.

- How are you controlling for or documenting a long Covid diagnosis?
—> We have not mentioned long COVID as it did not exist when the study was created. There is a free text box under past medical history, so should this have been documented as a diagnosis in more recent patients we would capture. Data about pre-ICU psychological distress before ICU admission (self-reported by patients as well as documented in medical notes) is being asked about.

- Here and for the other measures, I suggest a sample question. In looking at the measure, it is not clear that the traumatic event is the ICU stay. Just FYI, compare these 6 items to the Prins 5 yes/no items for primary care, which is quite similar but captures dissociation: Felt numb or detached from people, activities, or your surroundings?
—> We have been careful to apply the validated tools as they are, without adding any qualifying information. Due to copyright issues we cannot reproduce the questions.

- It is not clear how you are using these anxiety and depression data. Are they being correlated with HADS? Address the psychometric overlap of the EQ-5D-5L for the anxiety/depression domain with the HADS – will the anxiety/depression domain be left out?
—> When looking at predictive risk factors, we will use HADS scores not the anxiety/depression domain of EQ-5D-5L. We will be able to assess whether there is a correlation between the anxiety/depression domain of EQ-5D-5L and the HADS scoring.

- I could not find the 10-item scale but 1 reference refers to only 2 positive items. Unable to see what the coping items are. When you publish findings, perhaps you can add scales as additional content. Try to use public access measures so people can replicate your study.
—>The author of the CAS-1R questionnaire in particular has granted permission for the use of CAS-1R in the study but we are unable to reproduce the questions due to copyright limitations. We acknowledge that it is not ideal to use a questionnaire that is not widely available. This element of the study is exploratory though and is less integral to the study than the other scores, which are widely available. The psychologists who are part of the investigator team have experience with the CAS-1R score are therefore recommended it for its suitability to the exploratory question of whether positive/negative thought processes influence psychological outcomes.

- Is there a social vulnerability index for this? Deprivation compared to what? Need a reference to the Index
—> References have been added for the Deprivation Indices for England, Northern Ireland, Scotland and Wales.

The methods are not very clear. It will be easier to understand once you have some results. Can you provide some examples or illustrate what you think you will find and why the methods are appropriate for these kind of data.
—> The ‘Statistical Methods’ text has been reviewed and amended. The software that we plan to use has been added also.

VERSION 2 – REVIEW

REVIEWER	Didriksen, Maria Copenhagen University Hospital, Clinical Immunology
REVIEW RETURNED	04-May-2023

GENERAL COMMENTS	I read through the revised version of the study protocol now titled "PIM-COVID study: protocol for a multi-centre, longitudinal study measuring the psychological impact of surviving an intensive care admission due to COVID-19 on patients in the United Kingdom". I believe that after the revision, the protocol is suitable for publication.

REVIEWER	Grabbe, Linda Emory University, School of Nursing
REVIEW RETURNED	18-May-2023

GENERAL COMMENTS	Typos: pg 9 line 15 enrollment line 40 provide/give feedback Thank you for the revisions. Good luck on this important study.