PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a systematic review of interventions targeting mental health, cognition, or psychological wellbeing among individuals with long COVID
AUTHORS	Hawke, Lisa; Brown, Eric; Rodak, Terri; Rossell, Susan; Ski, Chantal; Strudwick, Gillian; Thompson, David; Wang, Wei; Xu, Dandan; Castle, David

VERSION 1 – REVIEW

REVIEWER	LOPES-JÚNIOR, LUÍS CARLOS Universidade Federal do Espirito Santo, Nursing Department
REVIEW RETURNED	19-May-2022

GENERAL COMMENTS	May 18, 2022 Thank you for the opportunity to review this timely article on an important topic on iinterventions targeting mental health, cognition, or psychological wellbeing among individuals with long COVID. Please find below some comments, suggestions in order to strengthen the potential contribution of this topic in any revision the author(s) might undertake. Since the authors are looking for interventions targeting mental health, cognition, or psychological wellbeing, the possible designs to be retrieved from the databases are clinical trials (RCN or Non-RCT [quasi-experimental studies]). In this regard, I recommend that the authors add an essential database which is The Cochrane Central Register of Controlled Trials (CENTRAL). In addition, it would be important to search RCT registry sites such as Clinical.Trial.gov and the WHO International Clinical Trials Registry Platform – as it should enhance searches. In addition, the new PRISMA Flowchart 2020 itself recommends this (databases and registers). Regarding the Eligibility criteria, on page 7, line 54, the authors state that “Any study design will be accepted”. This sentence needs to be revised as this is a protocol for experimental studies (that test interventions) so only the RCT and Non-RCT study designs should be included. In the same line of reasoning, for the methodological assessment of the risk of bias in the RCTs, the authors point out that the RoB-2 will be used. However, for Non-RCT you will need to add the ROBINS-I tool (BMJ 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919). Please, adjust these issues in the method.

REVIEWER	Kunzler, Angela Leibniz Institute for Resilience Research
REVIEW RETURNED	18-Jul-2022

GENERAL COMMENTS	Peer review – Protocol for a systematic review of interventions targeting mental health, cognition, or psychological wellbeing among individuals with long COVID (bmjopen-2022-063846) Thank you for the opportunity to review. The manuscript is a review protocol for a systematic review on interventions targeting mental health, cognition or psychological wellbeing among individuals suffering from long COVID. Given the various serious physical and mental symptoms observed in long COVID patients and its high prevalence, a systematic review on interventions to mitigate negative consequences for individuals diagnosed with long COVID seems worthwhile and highly relevant. Thus, a review protocol presenting details on this systematic review will likely be of interest to the readers of the journal and help to avoid double publications on the topic. In my opinion, the scope of the review is rather broad by investigating the efficacy, effectiveness, feasibility and acceptability of the interventions. At the same time, the eligibility criteria are a little unspecific, for example, regarding the types of interventions and the various outcomes that the authors plan to consider. Maybe it would be more appropriate to label the review as a scoping review since the authors plan to examine a broad research question and to explore the field of interventions. Please find my specific suggestions for each section below. Throughout the manuscript - Please check grammar and language through the manuscript. Abstract - Do you mean efficacy based on RCTs or really effectiveness? - “in” is missing before listing the various databases - It would be more appropriate to name the PRISMA guidelines in the first sentence of the ‘Methods and analysis’ section of the abstract and to provide more details about how study selection will be performed (since you will use the PRISMA guidelines for all stages of the review and not only for study selection). - . is missing behind “guidelines” - What is the difference between efficacy and effectiveness in your review? Especially since your review question seems to primarily focus on “effectiveness” (according to the introduction section of the abstract) - Instead of “methodological appraisal”, I would use the term “risk of bias assessment will be performed using…” and then cite the full name of the Cochrane RoB 2.0 tool - After reading the abstract, I am not sure if I understood the review aims correctly. Would you like to assess the efficacy and effectiveness of psychological interventions in individuals with long COVID (e.g., efficacy on mental health and wellbeing outcomes) along with their feasibility and acceptability? This could be stated more clearly. Introduction - Did the authors check for other completed or ongoing systematic reviews on their research question (e.g., in PROSPERO)? How does this review close a research gap?

	Objectives - Here and in other sections of the manuscript (e.g., title, abstract) you might consider to reformulate “interventions to foster/promote mental health, cognition, or psychological wellbeing”? Methods and analysis Reporting guidelines: - Delete “follow” Research question: - RQ 1 and RQ3 are probably overlapping since interventions to foster psychological wellbeing etc. are likely to assess this outcome as well, but this is rather a general remark. - In case your systematic review is rather of exploratory nature (e.g., provide a summary of the various available interventions and outcomes assessed) I would recommend to clarify this here. However, in case you plan to assess the efficacy of interventions, I would suggest being more specific about with respect to which outcomes (e.g., anxiety, depressive symptoms, wellbeing) you will examine the efficacy of the interventions. Types of interventions: - Why do you differ between ‘types of interventions’ and ‘eligibility criteria’? The type of intervention that you will consider is part of the PICO criteria, that is, the eligibility criteria. - Types of interventions: The protocol could benefit if you describe more precisely what kind of interventions you will include, for example, what do you refer to with “any aspect of mental health”? Will you include psychological interventions to prevent mental symptoms or mental disorders like anxiety or depressive disorders or only general interventions targeting positive mental health indicators like quality of life or wellbeing? Will you consider psychotherapy? What do you summarize under the term “cognition”? I would recommend being much more specific about your inclusion criteria here. - Please make 1-2 examples for outcomes of interest for the review. Will you differ between primary and secondary outcomes in our review? This would be important since you might limit meta-analyses (based on the available data) to the primary/main outcomes of your review that you define here (compare also PROSPERO structure for review protocols). - “Based on our existing review of registered trials…”: Does this mean you will include all these kinds of interventions? Please be more specific about this. - “Other types of interventions”: Could you give an example? Eligibility criteria: - It might be worthwhile to provide a Table presenting your eligibility criteria which is structured according to the PICO format (i.e., population, interventions, comparator, outcomes) in order to be more specific regarding your selection criteria (e.g., do you consider complex/multicomponent interventions as described in the introduction, which outcomes will you consider, what do you mean by “any study design”)? Which study design will be used to answer which of your review questions? For example, will you rely on RCTs to examine efficacy and on quantitative and qualitative studies to investigate feasibility and acceptability? Information sources: - Do you mean reference lists of included studies or also reference lists of other systematic reviews/meta-analyses? Search strategy: - What do you mean with “However, it cannot be thoroughly tested at this time due to paucity of literature on this topic to date. It will

	therefore be tested and iteratively refined and optimized as the literature emerges" Do you plan to conduct a living systematic review with regular updates? - P.8, l. 48-49: "placed" instead of "place" Table 2, data extraction plan: - The information that you will consider quantitative and qualitative studies (probably also mixed-methods studies?) and – within quantitative studies – controlled trials and longitudinal studies should be mentioned earlier under eligibility criteria. Could you give an example for physical and neuropsychological outcomes that might be relevant? I would already state this under 'eligibility criteria'. Outcomes and prioritization: - In my opinion, many of these information could already be given earlier under 'eligibility criteria' (e.g., in a Table). Please give examples for efficacy vs. effectiveness outcomes as well as for possible outcomes of feasibility and acceptability when you present your eligibility criteria and relevant types of outcomes. Data synthesis: - Which program will you use to perform the meta-analyses? Why do you choose random-effects modeling instead of fixed-effect modeling. Which information will you use to calculate SMDs or other effect estimates? How will you deal with missing information? Will you also consider further indicators of statistical heterogeneity or why do you focus on I2? Why do you focus on subgroup analyses regarding population characteristics (like gender and other sociodemographic variables)? Please be more specific which other sociodemographic variables you will consider. Do you also plan to perform subgroup analyses concerning intervention characteristics? How will you decide to perform subgroup analyses/meta-regression or not (e.g., based on the number of studies or the level of heterogeneity)? Please consider the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions to be more specific about your methodological decisions. - In case that you will not be able to perform meta-analyses (e.g., due to a small number of studies using a similar design or heterogeneity), your plan for a narrative synthesis could be described in more detail. For example, you could name the SWiM guidelines (https://swim.sphsu.gla.ac.uk/) which have been developed for this purpose. Assessment of study quality and bias: - What do you mean by "Generalizability indices will be calculated using the demographic characteristics of the identified samples…". Do you mean descriptive statistics like mean and SDs? Please be more specific. - Which sensitivity analyses do you plan to conduct? Will you exclude studies judged to be at high risk of bias? If so, please indicate which domains of bias you will use. - Will you also assess publication bias? Please justify if not. - Will you assess the certainty of evidence using GRADE? Please justify if not. Patient and public involvement: - Could you give an example for a "patient partner"? Limitations: - Depending on how you decide regarding some methodological procedures (e.g., certainty of evidence assessment), you could name further limitations. However, it might be worthwhile to also present some strengths of your review and how it might contribute to close a research gap. Conclusions

	- P14, l.50-51: important “for” PRISMA Checklist - If the PRISMA-P checklist is published along with the manuscript, please check the page numbers that you indicated. For example, according to the checklist, you described how the strength of the body of evidence will be assessed (e.g., using GRADE) on p. 13. However, this page (and the whole manuscript) does not contain this information. The same does apply to publication bias across studies.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. LUÍS CARLOS LOPES-JÚNIOR, Universidade Federal do Espirito Santo

Comments to the Author:
Thank you for the opportunity to review this timely article on an important topic on interventions targeting mental health, cognition, or psychological wellbeing among individuals with long COVID. Please find below some comments, suggestions in order to strengthen the potential contribution of this topic in any revision the author(s) might undertake.
- We thank the reviewer for their time and the valuable feedback provided.

Since the authors are looking for interventions targeting mental health, cognition, or psychological wellbeing, the possible designs to be retrieved from the databases are clinical trials (RCN or Non-RCT [quasi-experimental studies]).
- We have revised the protocol to be specific to clinical trials.

In this regard, I recommend that the authors add an essential database which is The Cochrane Central Register of Controlled Trials (CENTRAL).
In addition, it would be important to search RCT registry sites such as Clinical.Trial.gov and the WHO International Clinical Trials Registry Platform – as it should enhance searches. In addition, the new PRISMA Flowchart 2020 itself recommends this (databases and registers).
- We thank the reviewer for this suggestion and have added these sources.

Regarding the Eligibility criteria, on page 7, line 54, the authors state that “Any study design will be accepted”. This sentence needs to be revised as this is a protocol for experimental studies (that test interventions) so only the RCT and Non-RCT study designs should be included.
- We have edited this sentence accordingly.

In the same line of reasoning, for the methodological assessment of the risk of bias in the RCTs, the authors point out that the RoB-2 will be used. However, for Non-RCT you will need to add the ROBINS-I tool (BMJ 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919).
- We have added this tool as suggested.
Please, adjust these issues in the method.

Reviewer: 2
Dr. Angela Kunzler, Leibniz Institute for Resilience Research

Comments to the Author:
Thank you for the opportunity to review. The manuscript is a review protocol for a systematic review on interventions targeting mental health, cognition or psychological wellbeing among individuals

suffering from long COVID. Given the various serious physical and mental symptoms observed in long COVID patients and its high prevalence, a systematic review on interventions to mitigate negative consequences for individuals diagnosed with long COVID seems worthwhile and highly relevant. Thus, a review protocol presenting details on this systematic review will likely be of interest to the readers of the journal and help to avoid double publications on the topic.
- We appreciate the reviewer's time and attention to this manuscript, as well as the feedback that has enabled us to improve its quality.
In my opinion, the scope of the review is rather broad by investigating the efficacy, effectiveness, feasibility and acceptability of the interventions. At the same time, the eligibility criteria are a little unspecific, for example, regarding the types of interventions and the various outcomes that the authors plan to consider. Maybe it would be more appropriate to label the review as a scoping review since the authors plan to examine a broad research question and to explore the field of interventions.
- We thank the reviewer for these thoughts. After thorough consideration, we have decided to focus on clinical trials of efficacy rather than taking a broader approach that would align more with a scoping review methodology. We have revised the protocol to this effect.

Please find my specific suggestions for each section below.
Throughout the manuscript
- Please check grammar and language through the manuscript.

We have reviewed the paper for typographical errors and apologize for the errors that slipped through in the first version.

Abstract
- Do you mean efficacy based on RCTs or really effectiveness?
Revised

- "in" is missing before listing the various databases
Corrected

- It would be more appropriate to name the PRISMA guidelines in the first sentence of the 'Methods and analysis' section of the abstract and to provide more details about how study selection will be performed (since you will use the PRISMA guidelines for all stages of the review and not only for study selection).
Corrected
- . is missing behind "guidelines"
Sentence removed

- What is the difference between efficacy and effectiveness in your review? Especially since your review question seems to primarily focus on "effectiveness" (according to the introduction section of the abstract)
This has been clarified throughout, removing effectiveness.

- Instead of "methodological appraisal", I would use the term "risk of bias assessment will be performed using…" and then cite the full name of the Cochrane RoB 2.0 tool
Changed as requested

- After reading the abstract, I am not sure if I understood the review aims correctly. Would you like to assess the efficacy and effectiveness of psychological interventions in individuals with long COVID (e.g., efficacy on mental health and wellbeing outcomes) along with their feasibility and acceptability?

This could be stated more clearly.
Clarified (feasibility and acceptability has been removed)

Introduction
- Did the authors check for other completed or ongoing systematic reviews on their research question (e.g., in PROSPERO)? How does this review close a research gap?
There are currently no such reviews registered other than our own. We have described how this review will close the research gap regarding this emerging literature.

Objectives
- Here and in other sections of the manuscript (e.g., title, abstract) you might consider to reformulate "interventions to foster/promote mental health, cognition, or psychological wellbeing"?
Revised as suggested

Methods and analysis
Reporting guidelines:
- Delete "follow"
Corrected

Research question:
- RQ 1 and RQ3 are probably overlapping since interventions to foster psychological wellbeing etc. are likely to assess this outcome as well, but this is rather a general remark.
- We acknowledge the overlap. However, we do think it is important to keep RQ1, to describe the interventions that have been tested.

- In case your systematic review is rather of exploratory nature (e.g., provide a summary of the various available interventions and outcomes assessed) I would recommend to clarify this here. However, in case you plan to assess the efficacy of interventions, I would suggest being more specific about with respect to which outcomes (e.g., anxiety, depressive symptoms, wellbeing) you will examine the efficacy of the interventions.
- We have been more specific about efficacy and have described some of the outcomes.

Types of interventions:
- Why do you differ between 'types of interventions' and 'eligibility criteria'? The type of intervention that you will consider is part of the PICO criteria, that is, the eligibility criteria.
These have been merged into one section.

- Types of interventions: The protocol could benefit if you describe more precisely what kind of interventions you will include, for example, what do you refer to with "any aspect of mental health"? Will you include psychological interventions to prevent mental symptoms or mental disorders like anxiety or depressive disorders or only general interventions targeting positive mental health indicators like quality of life or wellbeing? Will you consider psychotherapy? What do you summarize under the term "cognition"? I would recommend being much more specific about your inclusion criteria here.
As per the description of the types of interventions, we will be quite inclusive of different types of interventions, including psychotherapy. Further information can be seen in our cited systematic review of registered trials. We believe we have clarified this appropriately.

- Please make 1-2 examples for outcomes of interest for the review. Will you differ between primary and secondary outcomes in our review? This would be important since you might limit meta-analyses (based on the available data) to the primary/main outcomes of your review that you define here (compare also PROSPERO structure for review protocols).

Table 3 describes the primary outcomes of interest as well as the secondary outcomes.

- “Based on our existing review of registered trials…”: Does this mean you will include all these kinds of interventions? Please be more specific about this.
- “Other types of interventions”: Could you give an example?
Yes, we do expect to include these interventions. We have clarified this section.

Eligibility criteria:
- It might be worthwhile to provide a Table presenting your eligibility criteria which is structured according to the PICO format (i.e., population, interventions, comparator, outcomes) in order to be more specific regarding your selection criteria (e.g., do you consider complex/multicomponent interventions as described in the introduction, which outcomes will you consider, what do you mean by “any study design”)? Which study design will be used to answer which of your review questions? For example, will you rely on RCTs to examine efficacy and on quantitative and qualitative studies to investigate feasibility and acceptability?

We have added the requested table, which we agree adds clarity. We have also clarified about the trial designs to be included.
Information sources:
- Do you mean reference lists of included studies or also reference lists of other systematic reviews/meta-analyses?
We have clarified this.

Search strategy:
- What do you mean with “However, it cannot be thoroughly tested at this time due to paucity of literature on this topic to date. It will therefore be tested and iteratively refined and optimized as the literature emerges” Do you plan to conduct a living systematic review with regular updates?
No, this is not a living review, merely the testing of the search strategy once literature is available to test it with. This has been clarified.

- P.8, l. 48-49: “placed” instead of “place”
Corrected

Table 2, data extraction plan:
- The information that you will consider quantitative and qualitative studies (probably also mixed-methods studies?) and – within quantitative studies – controlled trials and longitudinal studies should be mentioned earlier under eligibility criteria. Could you give an example for physical and neuropsychological outcomes that might be relevant? I would already state this under ‘eligibility criteria’.
We have limited the review to quantitative data from clinical trials. We have also pointed to potential neuropsychological outcomes depending on the data (pain, headache, and fatigue…).

Outcomes and prioritization:
- In my opinion, many of these information could already be given earlier under ‘eligibility criteria’ (e.g., in a Table). Please give examples for efficacy vs. effectiveness outcomes as well as for possible outcomes of feasibility and acceptability when you present your eligibility criteria and relevant types of outcomes.
We believe that the reorientation of the protocol, excluding effectiveness, addresses this concern.

Data synthesis:
- Which program will you use to perform the meta-analyses? Why do you choose random-effects

modeling instead of fixed-effect modeling. Which information will you use to calculate SMDs or other effect estimates? How will you deal with missing information? Will you also consider further indicators of statistical heterogeneity or why do you focus on I2? Why do you focus on subgroup analyses regarding population characteristics (like gender and other sociodemographic variables)? Please be more specific which other sociodemographic variables you will consider. Do you also plan to perform subgroup analyses concerning intervention characteristics? How will you decide to perform subgroup analyses/meta-regression or not (e.g., based on the number of studies or the level of heterogeneity)? Please consider the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions to be more specific about your methodological decisions.
We will use RevMan 5.4 for the meta-analyses. We hypothesized the trials that we are going to look at will have different underlying true effect and with that assumption, random-effects models are more appropriate than fixed-effects models (Tufanaru et al., 2015). For the standardized mean difference, we will use group mean difference and pooled standard deviation. We will also look at odds ratio and risk ratio as effect sizes for dichotomous outcome. As guided by Cochrane Handbook for Systematic Reviews of Interventions, we will focus on I2 as the indicator for statistical heterogeneity given that it is a well-accepted measure and relative easy to interpret. However, we acknowledge that many factors that cause this indicator to be misleading. The decision of perform subgroup analysis/meta-regression will be first driven by the research questions (e.g. gender effect). Meanwhile the number of studies that contains the subgroup information will determine whether the subgroup analyses is feasible.

- In case that you will not be able to perform meta-analyses (e.g., due to a small number of studies using a similar design or heterogeneity), your plan for a narrative synthesis could be described in more detail. For example, you could name the SWiM guidelines (https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Furldefense.com%2Fv3%2F__https%3A%2F%2Fswim.sphsu.gla.ac.uk%2F__%3B!!FxkXuJIC!Y8IOfvoOxt8NwQp9jNC9hn3Lvp0Ki02uduwAmtSIcD5SpIypgcfCD6LoJRvttw47xpizalnCaBPWWl14gqQeLtkbAUeOXA%24&data=05%7C01%7CC.Ski%40UOS.AC.UK%7C0b20a30219b0433ddebb08da68d708bb%7Cee265dd904ad41b7b409e6699705d35d%7C0%7C0%7C637937570022793081%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=amf%2Bc%2BuOmaDR4x7t%2BVEJUsEmlet72ykVAOwHO2piBvg%3D&reserved=0) which have been developed for this purpose.
We thank the reviewer for this and have added the SWiM guidelines.

Assessment of study quality and bias:
- What do you mean by “Generalizability indices will be calculated using the demographic characteristics of the identified samples…”. Do you mean descriptive statistics like mean and SDs? Please be more specific.
What we referred here are commonly used generalizability indices including C-statistics, SMD and Tipton’s index (Wang et al., 2017). These indices will reveal how different or similar the participants covered by the pooled studies and the general population of interest and provide a quantitative evaluation of how generalizable the meta-analysis results are.

- Which sensitivity analyses do you plan to conduct? Will you exclude studies judged to be at high risk of bias? If so, please indicate which domains of bias you will use.
Assuming that we will have K studies in total, the sensitivity analyses are repeated analyses of the primary analysis but with each of the K studies deleted from the pool one at a time. The resulting pooled effects of these K sensitivity analyses will then be compared with that of the primary analysis. This may identify highly influential studies.

- Will you also assess publication bias? Please justify if not.

This has been added.

- Will you assess the certainty of evidence using GRADE? Please justify if not.
This has been added.

Patient and public involvement:
- Could you give an example for a “patient partner”?
We have clarified this.

Limitations:
- Depending on how you decide regarding some methodological procedures (e.g., certainty of evidence assessment), you could name further limitations. However, it might be worthwhile to also present some strengths of your review and how it might contribute to close a research gap.
- We have added strengths.

Conclusions
- P14, l.50-51: important “for”
This has been removed, as per the editor’s request.

PRISMA Checklist
- If the PRISMA-P checklist is published along with the manuscript, please check the page numbers that you indicated. For example, according to the checklist, you described how the strength of the body of evidence will be assessed (e.g., using GRADE) on p. 13. However, this page (and the whole manuscript) does not contain this information. The same does apply to publication bias across studies.
This has been updated as requested.