PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol
AUTHORS	Lyons, Julia; Campese, Stephanie; Learmonth, Yvonne; Metse, Alexandra; Kermode, Allan; Karahalios, Amalia; Marck, C

VERSION 1 – REVIEW

REVIEWER	Moravejolahkami, Amir Reza Isfahan University of Medical Sciences, Clinical nutrition
REVIEW RETURNED	17-Sep-2021

GENERAL COMMENTS	Please response all the comments and highlight the changes. Please number the lines and pages for better finding of revisions. General comments to the Authors Congratulations. In general, the manuscript has been well written. The manuscript deals with an interesting protocol study across the MS trials. I suggest you apply numbering tool in word software, to clear subsections for each part. For example 1.1 or 2.1.2. …… I will address below comments to the study: Title: 1. The title is better to be modified: 'Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in patients with multiple sclerosis: a systematic review and network meta-analysis protocol, If you not agree, please explain. Abstract: 2. ABOUT KEYWORDS, please stick to these instructions: - Carefully select relevant keywords - Lead with keywords in the article title - Repeat keywords 3-4 times throughout the abstract - Use headings throughout the article - Include at least 5 keywords and synonyms in the keyword field 3. There are a lot of grammatical errors in the abstract (Misusing the words, use of the markers such as comma, etc). This is a serious problem, so you should fix the errors to make the manuscript ready for publication. Please stick to the journal instructions such as word count limit for abstract. 4. "Guidelines for ….."please rewrite this sentence so that it can be read better. 5. "randomized" not randomised. 6. "people with MS" is not formal in medical-based papers. Please write Patients with MS throughout the manuscript. 7. the third bullet point is not necessary. If you not agree, please explain

Introduction:
8. The introduction section is needed to be improved grammatically.
9. The sentence "Major depressive disorder …." has an inappropriate grammatical error by using comma.
10. The sentence "Further, the American …." has an inappropriate grammatical error.

Methods:
11. Material and methods are well-described and structured. The authors follows PRISMA guidelines.
12. subgroup not Sub-group
13. The biggest problem is search strategy. You should add another important databases such as pubmed, scopus, and google scholar. Moreover, the technique you used is inappropriate. In the sup material "SEARCH STATEGY TABLE" file, it is better to write the exact statement of search strategy in each database.
14. Which variables will be used for subgroup analysis? Please explain in a separate paragraph.
15. Can you check the publication bias? Which tests? Eager or …?
16. Can you explain about the plots that you will provide?
17. EDSS, type of MS (PPMS, PRMS, ….), type of drug , …. are the best variable for subgroup analysis. I suggest
18. The references are not up-to-date.

GOOD LUCK

REVIEWER	Masuccio, Fabio Giuseppe Department of Rehabilitation, CRRF. "Mons. L. Novarese"
REVIEW RETURNED	18-Dec-2021

GENERAL COMMENTS	A well-written and detailed protocol. I only suggest to add in the "Search strategy" paragraph - the dates since the search will be performed - one example of search line in at least one database

REVIEWER	Harrison, Anthony M University of Leeds, Clinical Psychology Training Programme, Institute of Health Sciences
REVIEW RETURNED	04-Jan-2022

GENERAL COMMENTS	Thank you for inviting me to review this protocol manuscript. Overall, I found it to be clearly written and sufficiently transparent to feel comfortable with it being published. However, I did have a few thoughts that might easily be addressed beforehand: -Could the authors perhaps provide some references for examples of treatments to help the reader who might not be familiar with them (page 9-10)? -I think explaining the transivity assumption more clearly earlier on would help the reader. You give an example related to treatment resistant depression and stepped careful ECT but it could still be a bit clearer. -When thinking about the categorisation of the different intervention groups on page 10, it is unclear if you plan to use any statistical techniques exploring heterogeneity (or other methods) to determine group membership. -Relatedly, might it be worth including the details of the intervention delivery using something like TIDieR (Hoffmann & Walker, 2015) -Would the authors consider extracting longer-term follow-up

outcomes (beyond 6 months), if available? In the real world, six months isn't really that long and it seems pertinent to give the message to those conducting RCTs the follow-up needs to be longer as a standard if they are persisting with no or limited follow-up timescales.

-When stating your outcomes on page 15, could you be more specific about some of these being depression symptoms?

-It might be more point for the discussion later but the overlap between symptoms of depression and fatigue are significant in this context, which are both highly prevalent. I would wonder if it would be important to consider ways to explore the impact of possible confounding and its impact on outcome. One thing to hold in mind, is whether a focus on reducing the impact of depression is sufficient.

I noticed a few minor errors/typos:

Page 6: To meet the transitivity assumption… in NMA
Page 8: Further, recent systematic reviews reported that exercise…

Otherwise, I look forward to hearing more about the results.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
General comments to the Authors Congratulations. In general, the manuscript has been well written. The manuscript deals with an interesting protocol study across the MS trials. I suggest you apply numbering tool in word software, to clear subsections for each part. For example 1.1 or 2.1.2. …… I will address below comments to the study:	We are pleased that the reviewer found our protocol interesting and well written. The reviewer's suggestion to number the headings does not align with the journal's guidelines, so we leave this decision to the editor.
Title: 1. The title is better to be modified: 'Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in patients with multiple	The inclusion criteria of our review does not state that participants of included studies are to be currently receiving care for multiple sclerosis. As such participants may not be patients with multiple sclerosis.

sclerosis: a systematic review and network meta-analysis protocol, If you not agree, please explain.	
Abstract: 2. ABOUT KEYWORDS, please stick to these instructions: - Carefully select relevant keywords - Lead with keywords in the article title - Repeat keywords 3-4 times throughout the abstract - Use headings throughout the article - Include at least 5 keywords and synonyms in the keyword field	The keywords included in our manuscript are: multiple sclerosis, depression, network meta-analysis and systematic review. However, when uploading the manuscript we are limited to predetermined keywords and have selected words from the scholar one system that appear most relevant. We leave this to the editor.
3. There are a lot of grammatical errors in the abstract (Misusing the words, use of the markers such as comma, etc). This is a serious problem, so you should fix the errors to make the manuscript ready for publication. Please stick to the journal instructions such as word count limit for abstract.	Thank you for your comment. We have reviewed the manuscript for grammatical errors and revised where appropriate. We have also ensured that use of acronyms is limited to frequently used acronyms. Finally, we have followed the journal's submission guidelines throughout and leave further stylistic issues to the editor.

4. "Guidelines for ….."please rewrite this sentence so that it can be read better.	This sentence has been changed to the following in the abstract (line 93-95: Guidelines for treating depression in people with MS suggest that a combination of psychological and pharmaceutical interventions is the most effective therapy in reducing levels of depressive symptoms
5. "randomized" not randomised.	We have used British English spelling throughout. We will leave this change to the editor's discretion.
6. "people with MS" is not formal in medical-based papers. Please write Patients with MS throughout the manuscript.	Please see our response to the reviewer's comment #1 above.
7. the third bullet point is not necessary. If you not agree, please explain	We have revised the third bullet point in the Strengths and Limitations section to (line 65-66): •*The review will aim to simultaneously compare intervention types that are used in both clinical and research settings.*
Introduction: 8. The introduction section is needed to be improved grammatically.	As noted in our response to comment #3, we have rechecked the manuscript and revised as necessary.
9. The sentence "Major depressive disorder …." has an inappropriate grammatical error by using comma.	As noted in our response to comment #3, we have rechecked the manuscript and revised as necessary.
10. The sentence "Further, the American …." has an inappropriate	As noted in our response to comment #3, we have rechecked the manuscript and revised

grammatical error.	as necessary.
Methods: 11. Material and methods are well-described and structured. The authors follows PRISMA guidelines.	Thank you for this comment.
12. subgroup not Sub-group	This change has been made throughout.
13. The biggest problem is search strategy. You should add another important databases such as pubmed, scopus, and google scholar. Moreover, the technique you used is inappropriate. In the sup material "SEARCH STATEGY TABLE" file, it is better to write the exact statement of search strategy in each database.	Selection of the included databases was done in consultation with a medical librarian. Embase, Medline and Web of Science have been shown to guarantee adequate and efficient coverage (Bramer et al 2017). Pubmed is a platform to search Medline, and we chose to search Medline through the Ovid platform. We chose not to include Google Scholar because searching general search engines (like Google Scholar) can introduce bias into the search methodology and the

	search is unlikely to be reproducible (Piasecki et al 2018). We have revised the description of the Search strategy to make it clear which platform was used for each database (e.g., the databases Medline and EMBASE were searched via the Ovid platform). By using a common platform (where appropriate), we were able to use the same search strategy for all databases searched within that platform. Bramer et al. "Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study". Systematic Reviews. 2017. 6:245. Piasecki et al. "Google search as an additional source in systematic reviews." Sci Eng Ethics. 2018. 24(2): 809-810.

14. Which variables will be used for subgroup analysis? Please explain in a separate paragraph.	The variables that we will use for subgroup analyses are listed below and are provided with more details in the section titled "Subgroup analysis" (lines 348-368):
	
	For the efficacy outcome, we will assess the following subgroups:
	
	    -year of baseline recruitment
	    -severity of depression at baseline
	    -self-reported vs clinical assessment
	    of the outcome

	-level of disability at enrolment
	    -whether the intervention was
	    conducted in a dose according to

appropriate guidelines.

For the safety and tolerability outcome we will assess year of baseline recruitment and level of disability at enrolment.

15. Can you check the publication bias? Which tests? Eager or …?	As noted in the manuscript (line: 370-374), we will assess small study effects using comparison-adjusted and contour-enhanced funnel plots. Egger's test is known to have low power and in a network meta-analysis it will be prone to the issues of multiple testing.
16. Can you explain about the plots that you will provide?	In the subsection 'Geometry of the network', we describe the network diagram that we will provide including what the nodes and edges in the network will represent.

	We have also made the following changes to the manuscript to ensure that it is clear what plots will be provided:
	1. We have moved the subsection 'Pairwise meta-analysis' to ensure that all methods that relate to the network meta-analysis model are presented in a coherent manner and included details of the statistical methods which will be used for the network meta-analysis model to differentiate this model to the one that will be fitted for pairwise meta-analysis.
	2. We have renamed the 'Summary statistics' subsection to 'Summary statistics and presentation of results' to make it clear that in this section we describe both aspects of reporting the results. In this section (lines 326-336), we describe the tables and figures that we will present. These include forest plots and a league table with the direct and network intervention effects, a predictive interval plot, and plots of the surface under the cumulative ranking curve (SUCRA).
17. EDSS, type of MS (PPMS, PRMS, ….), type of drug , …. are the best variable for subgroup analysis. I suggest	We have included a subgroup analysis by level of disability (i.e., disability progression). Level of disability and type of MS are highly correlated, so type of MS will not give us any information above that which we are already capturing using level of disability.
18. The references are not up-to-	We have reviewed the references and have

date. GOOD LUCK	made some changes.
Reviewer 2	
Comments to the Author: A well-written and detailed protocol. I only suggest to add in the "Search strategy" paragraph - the dates since the search will be performed - one example of search line in at least one database	We are pleased that the reviewer found our protocol detailed and well written. As also noted in our response to reviewer #1 (comment #3), we have added the dates that the of the search. We have provided comprehensive search strategies and followed the recommendations of PRISMA-S in the reporting of our search strategy (Rethlefsen

| | et al 2021ref). In response to reviewer #1's comment 13, we have revised our search strategy to make it clear when multiple databases are searched within a single platform.

Rethlefsen et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Systematic Reviews. 2021; 10 39. |
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| **Reviewer: 3** | |
| Thank you for inviting me to review this protocol manuscript. Overall, I found it to be clearly written and sufficiently transparent to feel comfortable with it being published. However, I did have a few thoughts that might easily be addressed beforehand:
-Could the authors perhaps provide some references for examples of treatments to help the reader who might not be familiar with them (page 9-10)? | We are again pleased that this reviewer found our protocol well written. We have revised the description of the interventions to include more examples. |
| -I think explaining the transivity assumption more clearly earlier on would help the reader. You give an example related to treatment resistant depression and stepped careful ECT but it could still be a bit clearer. | We have introduced and explained the transitivity assumption in the 2nd paragraph of the introduction to the paper as follows (line 112-118):

The major assumption underpinning network meta-analysis methods ensures that we can |

	compare two interventions via a third (common) intervention and is referred to as transitivity. Transitivity requires that the trials included in the network meta-analysis are considered to be 'jointly randomisable', that the common intervention (comparator) from the different trials is similar enough to be combined, and that the characteristics associated with the effect of the intervention are similar across the included trials (Salanti 2012 and Chaimani et al 2021)." We have also revised the methods section (lines 152-158) to provide clarity regarding the transitivity assumption and how we will assess the validity of this assumption in our network meta-analysis.

	Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods 2012; 3: 80–97.
	Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
-When thinking about the categorisation of the different intervention groups on page 10, it is unclear if you plan to use any statistical techniques exploring heterogeneity (or other methods) to determine group membership.	In line with current recommendations for conducting a network meta-analysis (Salanti 2012), categorisation of the intervention groups is based on content expertise (i.e., grouping interventions that are similar enough to be combinable) rather than relying on statistical techniques.
	Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods 2012; 3: 80–97.
-Relatedly, might it be worth including the details of the	We thank the reviewer for this suggestion. We will use the TIDieR as a guide to extract

intervention delivery using something like TIDieR (Hoffmann & Walker, 2015)	details on the included interventions in our review and to report on the details of each included intervention in our results paper. The following has been added to lines 234-235 the manuscript:
	We will use TIDieR for clear reporting of the characteristics of the interventions and comparators (Hoffmann et al).
	Hoffmann TC, Oxman AD, Ioannidis JP, et al. Enhancing the usability of systematic reviews by improving the consideration and description of interventions. BMJ 2017;358:j2998. doi: 10.1136/bmj.j2998

-Would the authors consider extracting longer-term follow-up outcomes (beyond 6 months), if available? In the real world, six months isn't really that long and it seems pertinent to give the message to those conducting RCTs the follow-up needs to be longer as a standard if they are persisting with no or limited follow-up timescales.	Thank you for this suggestion. We will extract data on efficacy and safety at 12 or more months post-intervention. The following has been added to lines 184-187 of the manuscript: *To measure long term efficacy and safety of interventions for reducing depressive symptoms we will also extract the relevant data that is measured 12 or more months post-intervention.*
-When stating your outcomes on page 15, could you be more specific about some of these being depression symptoms?	We have revised the manuscript first primary outcome as follows (lines 274-275): *Primary outcome:* 1. *Efficacy at reduction of depressive symptoms of intervention(s) at post intervention using standardised mean difference,* And added the following secondary outcomes (lines 284-287): *(3) efficacy of intervention (reduction of depressive symptoms) measured 12 months post-intervention (12 months or longer) and quantified using standardised mean differences;* *(4) safety of interventions (SAEs, AEs and tolerability) measured 12 months post-intervention (12 months or longer) and quantified using odds ratios.*
-It might be more point for the	We agree with the reviewer that there is

discussion later but the overlap between symptoms of depression and fatigue are significant in this context, which are both highly prevalent. I would wonder if it would be important to consider ways to explore the impact of possible confounding and its impact on outcome. One thing to hold in mind, is whether a focus on reducing the impact of depression is sufficient.

considerable overlap between symptoms of depression and fatigue. As well, we note in the introduction that one of the symptoms of major depressive disorder is fatigue. A recent network meta-analysis has assessed the efficacy of exercise and behavioural interventions to reduce fatigue in people with MS (Harrison et al 2021).

Our work will complement the paper by Harrison et al 2021 and we will ensure to discuss this further in the discussion section of our final manuscript.

Harrison et al. *Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A*

	network meta-analysis. Multiple Sclerosis Journal. 2021; 27(11): 1657-1678.
I noticed a few minor errors/typos: Page 6: To meet the transitivity assumption… in NMA	Thank you, changes have been made to the manuscript.
Page 8: Further, recent systematic reviews reported that exercise… Otherwise, I look forward to hearing more about the results.	Thank you, changes have been made to the manuscript.

VERSION 2 – REVIEW

REVIEWER	Harrison, Anthony M University of Leeds, Clinical Psychology Training Programme, Institute of Health Sciences
REVIEW RETURNED	22-Mar-2022

GENERAL COMMENTS	I feel that this manuscript should be published as the authors have, as far as I can tell, adequately addressed all of the points raised.