

## 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>	Comparative efficacy and safety of probiotics for the treatment of irritable bowel syndrome: a systematic review and network meta-analysis protocol
<b>AUTHORS</b>	Yang, Man; Yu, Yuanyuan; Lei, Ping-Guang; Yuan, Jinqiu

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Mohammad Abdollahi The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran
<b>REVIEW RETURNED</b>	01-Nov-2018

<b>GENERAL COMMENTS</b>	<p>Main concerns:</p> <p>Authors have included only MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials for their search while there would be found much more if PubMed and Google Scholar are added to the search databases.</p> <p>Also, authors have not specified whether the will be limitation is articles language. If languages other than English will be included, how will it be handled?</p> <p>I wonder why age under 18 years will be excluded? Many of IBS patients are among 14 to 18 years old.</p>
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<b>REVIEWER</b>	Joanna Harnett The University of Sydney
<b>REVIEW RETURNED</b>	29-Nov-2018

<b>GENERAL COMMENTS</b>	<p>Abstract</p> <p>Line 18 Typo – Safely should be Safety</p> <p>Line 21 Database Suggest adding CINAHL and Scopus to search method to ensure and add in search terms, key words</p> <p>Main document</p> <p>Typos throughout spell check required</p> <p>Inclusion/Exclusion criteria – It should be clarified what 'clinicians opinion' is based on. This inclusion criteria could result in a heterogeneous population with some participants falling outside of a true IBS diagnosis</p>
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<b>REVIEWER</b>	Cesare CREMON, MD University of Bologna, Bologna, Italy
<b>REVIEW RETURNED</b>	27-Feb-2019

<b>GENERAL COMMENTS</b>	This is a study protocol for a systematic review and network-meta-analysis assessing the comparative efficacy and safety of probiotics for the treatment of irritable bowel syndrome
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	<p>The protocol is clear and the study design and methodology appear sound.</p> <p>The main novelty of this work is the network meta-analysis of RCTs of probiotics in IBS as opposed to standard meta-analysis. In facts, several meta-analysis were performed on this topic in IBS, also recently (see Ford AC et al., Aliment Pharmacol Ther 2018;48:1044-1060). I suggest to better explain the novelty of this study and to expand the clinical relevance of this review for the reader.</p> <p>The background is poor and need to be updated. Similarly, the references need to be updated.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mohammad Abdollahi

Institution and Country: The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

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

Main concerns:

Authors have included only MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials for their search while there would be found much more if PubMed and Google Scholar are added to the search databases.

Response: Thank you. PubMed has the same data source as MEDLINE, so it is not necessary to search both. Google Scholar is currently not available in China, so it was not included in the database list. To make sure our search is comprehensive, we added another two databases, CINAHL and Scopus.

Also, authors have not specified whether the will be limitation is articles language. If languages other than English will be included, how will it be handled?

I wonder why age under 18 years will be excluded? Many of IBS patients are among 14 to 18 years old.

Response: Thank you. We will not limit the language. If we identified eligible studies which are reported with languages other than English, we will translate and then extract data.

The effectiveness of probiotics may be different between adults and patients under 18. We focus on adult's population because we plan to use network meta-analyses, which incorporate indirect comparison, and homogeneity is very important to obtain robust results.

Reviewer: 2

Reviewer Name: Joanna Harnett

Institution and Country: The University of Sydney

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

Abstract

Line 18 Typo – Safely should be Safety

Response: Thank you. We corrected this mistake and checked the reporting throughout the manuscript.

Line 21 Database Suggest adding CINAHL and Scopus to search method to ensure and add in search terms, key words

Response: Thank you we added these databases as suggested. The search terms and the complete search strategy for MEDLINE were reported in the manuscript.

Main document

Typos throughout spell check required

Response: Thank you. We asked a native speaker to check the manuscript.

Inclusion/Exclusion criteria – It should be clarified what 'clinicians opinion' is based on. This inclusion criteria could result in a heterogeneous population with some participants falling outside of a true IBS diagnosis

Response: Thank you. We agree that "clinician's opinion" is not specific and reliable. We excluded this statement.

Reviewer: 3

Reviewer Name: Cesare CREMON, MD

Institution and Country: University of Bologna, Bologna, Italy

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

This is a study protocol for a systematic review and network-meta-analysis assessing the comparative efficacy and safety of probiotics for the treatment of irritable bowel syndrome

The protocol is clear and the study design and methodology appear sound.

The main novelty of this work is the network meta-analysis of RCTs of probiotics in IBS as opposed to standard meta-analysis. In facts, several meta-analysis were performed on this topic in IBS, also recently (see Ford AC et al., Aliment Pharmacol Ther 2018;48:1044-1060). I suggest to better explain the novelty of this study and to expand the clinical relevance of this review for the reader.

The background is poor and need to be updated. Similarly, the references need to be updated.

Response: Thank you. Through several meta-analyses have been carried out (we have cited them in the manuscript. Ref 8 & 9), these studies did not evaluate the comparative effect of individual combination, species or strains of probiotics. These systematic reviews also indicated that "... which individual species and strains are the most beneficial remains unclear." This study will focus on the comparative effect rather than the overall effect. In addition, several RCTs have been published recently but were included in these meta-analyses. It is necessary to perform a new systematic review to address these problems.

We revised the background and highlighted the novelty and importance of the current systematic review.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Mohammad Abdollahi The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran
<b>REVIEW RETURNED</b>	21-Jul-2019

<b>GENERAL COMMENTS</b>	<p>I would like to ask authors to know that "PubMed" the freely available medical indexing database is more complete than the "Medline". This means that anything exists in Medline can be found in PubMed but with a greater coverage and the chance to find many more relevant studies. In addition, EMBASE is included in the Scopus meaning that if Scopus is searched, there will be no need to recheck the EMBASE.</p> <p>Also, another article has been newly published about the safety of probiotics where their new contraindications and adverse effects have been stated. Authors may get benefit of reading that: Reappraisal of probiotics' safety in human. Food Chem Toxicol. 2019 Jul;129:22-29. doi: 10.1016/j.fct.2019.04.032. Epub 2019 Apr 19. Review. PubMed PMID: 31009735.</p>
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<b>REVIEWER</b>	Joanna Harnett The University of Sydney, Australia
<b>REVIEW RETURNED</b>	25-Jul-2019

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review your protocol. The question you are endeavouring to answer is a very important clinical question for clinicians and people living with IBS.</p> <p>General comments: The standard of English requires revising in some areas of the manuscript. The use of past, present and future tense needs to be standardised across the paper.</p> <p>There are a number of small but distracting typographical errors e.g. page 5 line 38 the word 'lasted' should be replaced with 'latest'.</p> <p>As a suggestion I would perhaps adopt a hierarchical order to describe what you are including i.e. genus, species, strain. Probiotic strain is not a common term used in the literature. e.g. 'strain specific species of probiotic bacteria or yeasts' is probably a better scientific description. You can't just report a strain without the species.</p> <p>Methods: Page 6 inclusion and exclusion criteria does not include the Rome IV criteria. Is there a reason for this?</p> <p>Page 7 line 35 - consider including studies that used Cognitive Behavioural Therapy as a control.</p> <p>Page 57 line 51 - what do you mean by 'accept a different standard' perhaps this could be made clearer.</p> <p>Page 57 line 56 - what is the scientific rationale for excluding studies that were less than one week's duration.</p> <p>Line 4 page 8 - missing word.</p> <p>Search Terms:</p> <p>I am unclear why you included brand/trade names in your search? Wouldn't all the bacteria and yeast listed in the search capture studies that evaluated specific products? There is also a risk of bias introduced when including some but not all brand/trademark names.</p> <p>I hope this feedback is helpful in refining your protocol.</p>
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<b>REVIEWER</b>	Cesare CREMON, MD University of Bologna, Bologna, ITALY
<b>REVIEW RETURNED</b>	29-Jul-2019
<b>GENERAL COMMENTS</b>	The manuscript has been improved. Thank you for this revision.

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mohammad Abdollahi

Institution and Country: The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

Please state any competing interests or state 'None declared': No competing interests

I would like to ask authors to know that "PubMed" the freely available medical indexing database is more complete than the "Medline". This means that anything exists in Medline can be found in PubMed but with a greater coverage and the chance to find many more relevant studies. In addition, EMBASE is included in the Scopus meaning that if Scopus is searched, there will be no need to recheck the EMBASE.

Response: Thank you. We revised the method and included PubMed and Scopus. The search strategy was also updated.

Also, another article has been newly published about the safety of probiotics where their new contraindications and adverse effects have been stated. Authors may get benefit of reading that: Reappraisal of probiotics' safety in human. Food Chem Toxicol. 2019 Jul;129:22-29. doi: 10.1016/j.fct.2019.04.032. Epub 2019 Apr 19. Review. PubMed PMID: 31009735. Response: Thank you for the recommendation. We read this paper. This paper provide an comparehenvie summay of the safety for probiotics, which is very helpful for our manuscript. We cited this paper in the background.

Reviewer: 2

Reviewer Name: Joanna Harnett

Institution and Country: The University of Sydney, Australia

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

Thank you for the opportunity to review your protocol. The question you are endeavouring to answer is a very important clinical question for clinicians and people living with IBS.

General comments: The standard of English requires revising in some areas of the manuscript. The use of past, present and future tense needs to standardised across the paper.

There are a number of small but distracting typographical errors e.g. page 5 line 38 the word 'lasted' should be replaced with 'latest'.

Response: Thank you very much. I revised the manuscript. I addition to these problems, we also invited a native speaker from Malaysia to check the English throughout the manuscript.

As a suggestion I would perhaps adopt a hierarchal order to describe what you are including i.e. genus, species, strain. Probiotic strain is not a common term used in the literature. e.g. 'strain specific species of probiotic bacteria or yeasts' is probably a better scientific description. You can't just report a strain without the species.

Response: Thank you. We accepted your suggestion and revised the reporting of probiotics.

Methods: Page 6 inclusion and exclusion criteria does not include the Rome IV criteria. Is there a reason for this?

Response: Thank you. Rome IV criteria should also be eligible. We added to the manuscript.

Page 7 line 35 - consider including studies that used Cognitive Behavioural Therapy as a control.

Response: Thank you very much for your suggestion. Including Cognitive Behavioural Therapy will increase the scope of this study. However the primary objective is to evaluate the comparative effect of various species of probiotics and combination regimens for the treatment of IBS using network meta-analysis. Network meta-analysis calculate the indirect comparison via common comparators, so the effect of common comparators should ideally be same across included studies. This is the reason why we only included placebo, no treatment as the comparators/control. Cognitive Behavioural Therapy is often used in clinical trials but it may not be identical among different studies. These difference may introduce bias to the direct comparison. So we prefer to not include Cognitive Behavioural Therapy. We explained this in the methods.

Page 7 line 51 - what do you mean by 'accept a different standard' perhaps this could be made clearer.

Response: Thank you. Currently, many different standards are used for the assessment of IBS symptoms in clinical trials. There will be no limitation on the IBS symptoms assessment standard in this systematic review. We explained this in the methods.

Page 57 line 56 - what is the scientific rationale for excluding studies that were less than one weeks duration.

Response: Thank you. IBS is a chronic condition and treatment often require long time to take effect. A clinical trial with <1 week treat is unable to fully demonstrate the true effect of probiotics. We explained this in the methods.

Search Terms:

I am unclear why you included brand/trade names in your search? Wouldn't all the bacteria and yeast listed in the search capture studies that evaluated specific products? There is also a risk of bias introduced when including some but not all brand/trademark names.

Response: Thank you. We agree that bacteria and yeast listed in the search could capture studies that evaluated specific products. We removed the brand/trade names as suggested.

I hope this feedback is helpful in refining your protocol.

All the best

Joanna Harnett

Reviewer: 3

Reviewer Name: Cesare CREMON, MD

Institution and Country: University of Bologna, Bologna, ITALY

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

The manuscript has been improved. Thank you for this revision.

Response: Thank you very much.