PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Neonatal Encephalopathy: a systematic review of reported treatment outcomes
AUTHORS	Quirke, Fiona Biesty, Linda Battin, Malcolm Bloomfield, Frank Daly, Mandy Finucane, Elaine Healy, Patricia Hurley, Tim Kirkham, Jamie J. Molloy, Eleanor Haas, David M. Meher, Shireen Ní Bhraonáin, Elaine Walker, Karen Webbe, James Devane, Declan

VERSION 1 - REVIEW

REVIEWER NAME	Dr. Ela Chakkarapani
REVIEWER AFFILIATION	University of Bristol School of clinical sciences St Michael's Hospital Level D Southwell street Bristol BS2 8EG United Kingdom of Great Britain and Northern Ireland Phone: 01173425711
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	10-May-2024

GENERAL COMMENTS	Quirke et al, in their article Neonatal Encephalopathy: a systematic review of reported treatment outcomes, report the heterogeneity of outcomes reported in randomised clinical trials and systematic reviews of interventions investigated for the treatment of neonatal encephalopathy. This manuscript has already been subjected to peer review with response to the review. I am providing additional review. The article is concise and answers the research question

	asked. Some suggestions to improve the manuscript. 1. Abstract: The background does not have the objective for the study. Introduction 2. Page 11, Please provide reference for the statement many studies measure and report different outcomes to determine the effectiveness of treatments. 3. How this manuscript fits in the pipeline of developing COS and why this work is needed for COS needs to be there in the introduction. 4. What criteria was used to exclude the 3955 titles? 5. limitation: 116 excluded as full text was not available. What efforts were put in to procure those full texts? 6. Discussion: please include the number of participants in the qualitative interview and how the saturation was achieved. Ref 131. 7. The introduction should give a robust justification for the COS and the impact studies using COS have had on patient care or health policy. If none exist, then, please acknowledge it in the limitations. 8. How does the methodology of having key stakeholders prioritising the outcomes make the COS robust? How are the key stakeholders chosen? How is the bias, conflicts of interest assessed and addressed? While I appreciate a need for COS, I do not see a justification or critical appraisal of methodologies employed to arrive at the COS in the manuscript.

REVIEWER NAME	Dr. Shripada Rao
REVIEWER AFFILIATION	Perth Children's Hospital Neonatal paediatrics Hospital avenue Nedlands Western Australia 6009 Australia
REVIEWER CONFLICT OF INTEREST	No
DATE REVIEW RETURNED	19-May-2024

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript that has been revised after adequately addressing other previous reviewers' comments. It is a well conducted systematic review and a well-written manuscript. However, I have concerns about the concept of enforcing COS on researchers. 1. I agree that it is important to provide guidance for future researchers on important outcomes in RCTs of HIE/NE. However, it is unreasonable to enforce that COS should always be measured and reported [page 58, line 26-27 in the clean version]. RCTs with limited funding may want to focus on short term outcomes. Some RCTs may be interested in exploring

	biochemical pathways of a new intervention. To enforce them to report COS can stifle innovative ideas and undemocratize research. Moreover, it is unreasonable to expect that a COS established by a group of experts and few parents' opinions will reflect the majority population's opinion. It is important to discuss the pros and cons of COS in the discussion section of this systematic review to provide a holistic viewc, since systematic reviews are the first step towards establishing COS. 2. The debate about terms "neonatal encephalopathy" vs "hypoxic ischemic encephalopathy" is ongoing. Whilst the term HIE is not perfect, it is a familiar name that has been in use for many decades. Thus "neonatal encephalopathy" is another imperfect term to replace the previous imperfect but familiar term. A brief note in the introduction justifying the reason for using the term NE would be useful. Minor comment: Page 13 Line 11 Outcome: All outcomes (related to the effect of the intervention) will be included. It should be "were included".

VERSION 1 – AUTHOR RESPONSE

Dear Reviewers,

On behalf of the COHESION team, I would like to thank you for your feedback and recommendations from this manuscript. We appreciate your input and have addressed comments below and in the manuscript.

Kind Regards,
Fiona Quirke

Formatting Amendments (where applicable):

1) Missing Grant Number

You have indicated a funder/s for your paper. Please ensure to provide an award/grant number for your funder/s in the submission system.
If the funder cannot provide an award/grant number, you can indicate N/A for the award/grant number.

This has been updated.

2) Author Correspondence Mismatch

The corresponding author stated in the main document does not match the corresponding author declared in the ScholarOne submission system. Kindly rectify by ensuring both authors and their email addresses match

The corresponding author is Fiona Quirke 22306056@studentmail.ul.ie

3) Different Funding Statement

Upon checking your manuscript, I noticed that the Finding Statement in the main documents and funder listed in the system is different. Kindly update your records and ensure that all data provided in the system should be matched in your main document file.

This has been corrected.

4) Supplementary File Format

Please be advised that supplemental materials and appendices included with the manuscript must be uploaded in PDF format. Kindly convert the supplemental file/s in the submission to PDF and re-upload.

5) Author Names

Please check on the Author's names in the main document and in the system below. The names indicated in the main document must match the name registered in the ScholarOne submission system.

System: Bloomfield, Frank Harry
Main Document: Frank H. Bloomfield

This has been corrected.

Reviewer: 1
Dr. Ela Chakkarapani, University of Bristol
Comments to the Author
Quirke et al, in their article Neonatal Encephalopathy: a systematic review of reported treatment outcomes, report the heterogeneity of outcomes reported in randomised clinical trials and systematic reviews of interventions investigated for the treatment of neonatal encephalopathy.

This manuscript has already been subjected to peer review with response to the review. I am providing additional review.

The article is concise and answers the research question asked. Some suggestions to improve the manuscript.

1. Abstract: The background does not have the objective for the study.

The objective has been included in the abstract.

Introduction
2. Page 11, Please provide reference for the statement many studies measure and report different outcomes to determine the effectiveness of treatments.
This statement was in relation to the findings from this systematic review.

3. How this manuscript fits in the pipeline of developing COS and why this work is needed for COS needs to be there in the introduction.
This is mentioned in the last paragraph of the introduction.

4. What criteria was used to exclude the 3955 titles?
Clarified that excluded titles were those that did not meet the PICOS criteria.

5. limitation: 116 excluded as full text was not available. What efforts were put in to procure those full texts?
This was clarified on page 10

6. Discussion: please include the number of participants in the qualitative interview and how the saturation was achieved. Ref 131.
This has been included on page 12.

7. The introduction should give a robust justification for the COS and the impact studies using COS have had on patient care or health policy. If none exist, then, please acknowledge it in the limitations.
Thank you for this comment, we have addressed this in the COS paper more specifically as the purpose of this paper is not to describe the COS itself but to outline the heterogeneity in outcomes informing the COS development.

8. How does the methodology of having key stakeholders prioritising the outcomes make the COS robust? How are the key stakeholders chosen? How is the bias, conflicts of interest assessed and addressed? While I appreciate a need for COS, I do not see a justification or critical appraisal of methodologies employed to arrive at the COS in the manuscript.
Thank you for this comment. This again relates more specifically to papers we have published on the

COS development process overall and is not the specific aim of this systematic review (i.e. to establish the heterogeneity in outcomes reported)

Reviewer: 2
Dr. Shripada Rao, Princess Margaret Hospital for Children
Comments to the Author
Thank you for the opportunity to review this manuscript that has been revised after adequately addressing other previous reviewers' comments.
It is a well conducted systematic review and a well-written manuscript. However, I have concerns about the concept of enforcing COS on researchers.

1. I agree that it is important to provide guidance for future researchers on important outcomes in RCTs of HIE/NE. However, it is unreasonable to enforce that COS should always be measured and reported [page 58, line 26-27 in the clean version].
RCTs with limited funding may want to focus on short term outcomes. Some RCTs may be interested in exploring biochemical pathways of a new intervention. To enforce them to report COS can stifle innovative ideas and undemocratize research. Moreover, it is unreasonable to expect that a COS established by a group of experts and few parents' opinions will reflect the majority population's opinion. It is important to discuss the pros and cons of COS in the discussion section of this systematic review to provide a holistic viewc, since systematic reviews are the first step towards establishing COS.

Thank you for this comment, we do take your thoughts on board. The methodologies used to develop the COS involved input from a large number of individuals and was open for global participation. As we have followed the guidance and methodologies for developing the COS we do believe in its applicability. We do accept that resources may be limited and had robust discussions around this with participants from Low-to middle income countries as well as High-income countries in developing the COS. We suggest that in order to be able to conduct a meta-analysis which is in the best interest of patients, researchers should attempt to measure the outcomes outlined in the COS. Where this is not possible for reasons such as resources, they should also be transparent in reporting the rationale for not measuring and reporting certain outcomes.

2. The debate about terms "neonatal encephalopathy" vs "hypoxic ischemic encephalopathy" is ongoing. Whilst the term HIE is not perfect, it is a familiar name that has been in use for many decades. Thus "neonatal encephalopathy" is another imperfect term to replace the previous imperfect but familiar term. A brief note in the introduction justifying the reason for using the term NE would be useful.

We agree that the terminology is the focus of much debate. The rationale for using the term neonatal encephalopathy was to include RCTs for treatments for conditions other than HIE that have been described as Neonatal encephalopathy. This is outines in our inclusion criteria: Population: Infants diagnosed and treated for neonatal encephalopathy, hypoxic ischemic or perinatal asphyxia/ birth asphyxia encephalopathy; infants greater than or equal to 35 weeks' gestation.

3. Minor comment: Page 13 Line 11 Outcome: All outcomes (related to the effect of the intervention) will be included. It should be "were included".

This has been amended.