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

TITLE (PROVISIONAL)	The prevalence and incidence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Europe: the Euro-epiME study from the European network EUROMENE. A protocol for a systematic review.
AUTHORS	Estévez-López, Fer; Castro-Marrero, Jesus; Wang, Xia; Bakken, Inger Johanne; Ivanovs, Andrejs; Nacul, Luis; Sepulveda, Nuno; Strand, Elin; Pheby, Derek; Alegre, Jose; Scheibenbogen, Carmen; Shikova-Lekova, Evelina; Lorusso, Lorenzo; Capelli, Enrica; Slobodan, Sekulic; Lacerda, Eliana; Murovska, Modra

VERSION 1 – REVIEW

REVIEWER	Elizabeth R. Unger Centers for Disease Control and Prevention, United States of America
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	The manuscript provides a protocol developed by the epidemiology workgroup of the European Network on ME/CFS (EUROMENE) to conduct a systematic review of published and grey literature on the incidence and prevalence of ME/CFS in all age groups in European countries. The protocol is clearly described and the approach conforms to accepted guidelines. The results of the systematic review will be helpful in guiding further work of EUROMENE. Just a few comments: 1. Another strength of the study: An established working group that is substantially representative of the European ME/CFS clinical/research community is conducting the study. This will increase the reliability and credibility of the findings. 2. Use of the term “validated” ME/CFS case definitions in description of strengths and limitations could be questioned. One of the goals of ME/CFS research is to improve and validate research and clinical case definitions. Perhaps “currently accepted” could be substituted in this section, with a fuller description in the paper. In the final publication is will be clear which case definitions are used and which were not accepted. 3. The authors may want to consider a fuller description of ME/CFS in the abstract since that will be the most widely read portion of the manuscript. The current description focuses only on fatigue and may perpetuate misunderstanding of the complexity of ME/CFS.

REVIEWER	A Chaudhuri Queen's Hospital, United Kingdom
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The article by Estévez-López and colleagues is a protocol of research intent and not a completed research manuscript. There are

	two major shortcomings of the proposed research protocol: broad clinical diagnostic criteria of ME/CFS (medically unexplained chronic fatigue of at least six months and impact on functional status) and unselected patient population from primary care where diagnostic accuracy is not infallible. The authors are only looking at prevalence of ME/CFS in their studies (section on methods) but it is not clear how they will estimate the incidence which is one of the questions they are attempting to answer from their research. I have reservations in their open time frame for literature search. The diagnosis of ME/CFS and the estimate of the disease prevalence are likely to be influenced by the choice of diagnostic criteria which have evolved over the years. Researchers may question if the ME/CFS patient population selected by Oxford criteria, as an example, is the same as the population of ME/PVFS diagnosed six months after a viral illness in a community clinic. It defies logic as to why those patients developing ME/CFS after a viral infection would be excluded and how such exclusion will aid the estimate of ME/CFS incidence in the population. Indeed, there are already serious selection biases in the protocol, which will severely limit usefulness of the research data. Use of post-exertional malaise (PEM) for 24 hours or longer is a useful symptom to distinguish ME/CFS from other conditions of chronic fatigue. My final comment is about the intended search to be restricted to 'European" countries and presumably to publications in English (based on their search strategy). This would not be truly representative of European population if migrant data are not separated and publications in local language (e.g. Croatian or Romanian) are not searched. A prospective (rather than the retrospective, as authors propose) population research with pre-defined case selection for ME/CFS across major European collaborating centres will yield far more useful information of clinical and scientific value.

REVIEWER	Derek Enlander Md Mount Sinai Medical Center
REVIEW RETURNED	07-Apr-2018

GENERAL COMMENTS	Would appreciate comparison of criteria selected and comments on patients selected by these criteria Comment on. Why the Oxford Criteria were not acceptable. ..... I agree the Oxford criteria are not acceptable but a comment is warranted

VERSION 1 – AUTHOR RESPONSE

Reviewer's 1 (i.e., Elizabeth R. Unger, PhD) comments to the authors:
****

General comments
The manuscript provides a protocol developed by the epidemiology workgroup of the European Network on ME/CFS (EUROMENE) to conduct a systematic review of published and grey literature on the incidence and prevalence of ME/CFS in all age groups in European countries. The protocol is

clearly described and the approach conforms to accepted guidelines. The results of the systematic review will be helpful in guiding further work of EUROMENE.
Response.
Thank you for your compliments and thoughtful review.

Specific comments (1)
Another strength of the study: An established working group that is substantially representative of the European ME/CFS clinical/research community is conducting the study. This will increase the reliability and credibility of the findings.
Response.
Thanks for highlighting this strength. The 'Strengths and limitations' has been modified accordingly [see, page 5, lines 80-83].

Specific comments (2)
Use of the term "validated" ME/CFS case definitions in description of strengths and limitations could be questioned. One of the goals of ME/CFS research is to improve and validate research and clinical case definitions. Perhaps "currently accepted" could be substituted in this section, with a fuller description in the paper. In the final publication is will be clear which case definitions are used and which were not accepted.
Response.
We fully agree, thanks for catching this [see, page 5, line 76].

Specific comments (3)
The authors may want to consider a fuller description of ME/CFS in the abstract since that will be the most widely read portion of the manuscript. The current description focuses only on fatigue and may perpetuate misunderstanding of the complexity of ME/CFS.
Response.
Done [see, page 3, lines 42-49].

****
Reviewer's 2 (i.e., A Chaudhuri, PhD) comments to the authors:
****

Specific comments (1)
The article by Estévez-López and colleagues is a protocol of research intent and not a completed research manuscript.
Response.
The reviewer is right, indeed, we submitted our work as a protocol paper. To publish protocol of research intent enhances transparency, reduces publication bias, prevents selective publication and selective reporting of research outcomes, and prevents unnecessary duplication of research.
Specific comments (2)
There are two major shortcomings of the proposed research protocol: broad clinical diagnostic criteria of ME/CFS (medically unexplained chronic fatigue of at least six months and impact on functional status) and unselected patient population from primary care where diagnostic accuracy is not infallible.
Response.
Thank you.
Regarding the diagnostic criteria, our 3rd and 4th exclusion criteria indicate that we will exclude 'studies based on self-report of the diagnosis of ME/CFS' and 'Studies with an inappropriate case definition (e.g., CFS-like illness or other clinical criteria, such as the Oxford criteria due to lack of specificity)', respectively. This will lead to include previous studies than rely on currently accepted case definitions of ME/CFS.

Regarding primary care settings, we fully agree with the reviewer. Indeed, misdiagnosis of ME/CFS in primary care settings reflects a main caveat in the current state of the field. Therefore, the interpretation of our findings will be modest and in line with such a limitation. EUROMENE is both an ambitious and realistic network. The proposed review is a first valuable step in which will provide a picture of the current situation. Accordingly, we will highlight the challenges to overcome in the upcoming years, in which we hope that EUROMENE will play a key role.

Specific comments (3)
The authors are only looking at prevalence of ME/CFS in their studies (section on methods) but it is not clear how they will estimate the incidence which is one of the questions they are attempting to answer from their research.
Response.
Thank you for catching this. The word 'incidence' [page 8, line 136] and was missed in the 1st inclusion criteria and at the end of the sub-heading 'data synthesis and analysis' [page 11, line 209], now it has been added.

Specific comments (4)
I have reservations in their open time frame for literature search. The diagnosis of ME/CFS and the estimate of the disease prevalence are likely to be influenced by the choice of diagnostic criteria which have evolved over the years. Researchers may question if the ME/CFS patient population selected by Oxford criteria, as an example, is the same as the population of ME/PVFS diagnosed six months after a viral illness in a community clinic. It defies logic as to why those patients developing ME/CFS after a viral infection would be excluded and how such exclusion will aid the estimate of ME/CFS incidence in the population. Indeed, there are already serious selection biases in the protocol, which will severely limit usefulness of the research data. Use of post-exertional malaise (PEM) for 24 hours or longer is a useful symptom to distinguish ME/CFS from other conditions of chronic fatigue.
Response.
A time frame of 10 years for the literature search will allow us to include papers from five years before the latest published literature review. Accordingly, we have included another exclusion criterion; i.e., 'Studies published more than 10 years ago (i.e., before 2008)' [page 8, line 150]. As the reviewer points out, the choice of diagnostic criteria has evolved over the years, and we consider that new period added to the inclusion criteria might help to minimise selection biases. The remaining differences and the implication for the findings will be thoroughly discussed, and when possible sensitivity analyses will be performed to better understand the true changes over time. Unfortunately, information on post-exertional malaise will only be available in a minority of studies, and including only papers which cover this topic will strongly reduce the body of available knowledge. Given that the reviewer's concerns about the potential sources of heterogeneity, we have been more specific in the inclusion criteria for the clinical diagnosis (i.e., 'Studies reporting either the prevalence or incidence of ME/CFS, including any of the following clinical diagnostic criteria – CDC-1994 [9], Canadian Consensus Criteria [1], London Criteria [21], International Consensus Criteria [10], or Institute of Medicine criteria [22], irrespective of age groups'; see page 8, lines 136-139]), and added more information about how we will manage the heterogeneity narratively [page 10, lines 203-205] and quantitatively [page 11, lines 209-211].

Specific comments (5)
My final comment is about the intended search to be restricted to 'European" countries and presumably to publications in English (based on their search strategy). This would not be truly representative of European population if migrant data are not separated and publications in local language (e.g. Croatian or Romanian) are not searched.
Response.
Although maybe under represented, PubMed, Scopus, and Web Of Science index journal in non-English languages. We would like also to note that our protocol includes a twofold complementary

search. First, we will check the reference lists of the included papers and their citations (i.e., backward- and forward-search). Second, all the members of EUROMENE will provided available data on prevalence or incidence rates of ME/CFS in their countries. Therefore, our search will summarise both the English and non-English literature.
According with the reviewer concern on migrants, the number of migrants (and % of the total sample) of the included studies will be registered –if available-, which potentially will allow us to discuss the heterogeneity of our findings [see, page 10, line 190]. Thanks.

Specific comments (6)
A prospective (rather than the retrospective, as authors propose) population research with pre-defined case selection for ME/CFS across major European collaborating centres will yield far more useful information of clinical and scientific value. Response.
To conduct such research will definitely yield to better estimate the prevalence and incidence of ME/CFS in Europe. However, this research takes time and requires much more resources. Meanwhile and given that the last systematic review as conducted more than 5 years ago, did not report the incidence of ME/CFS, and did not include children or adolescents, our review will be informative. Additionally, if our findings will support the reviewer's appraisal, we could ask for further funding for conducting such type of research.

****
Reviewer's 3 (Derek Enlander, MD) comments to the authors:
****

Specific comment (1)
Would appreciate comparison of criteria selected and comments on patients selected by these criteria Response.
Thanks for catching this. We have been more clear about which diagnostic criteria will be consider; i.e., 'Studies reporting either the prevalence or incidence of ME/CFS, including any of the following clinical diagnostic criteria – CDC-1994 [9], Canadian Consensus Criteria [1], London Criteria [21], International Consensus Criteria [10], or Institute of Medicine criteria [22], irrespective of age groups [see, page 8, lines 136-139]. Additionally, when we publish the review, we will take into account the reviewer's though. Accordingly, the following sentence has been added to the protocol: 'We will discuss whether the prevalence or incidence of ME/CFS differ according to the case definition used to examine the figures' [see, page 10, lines 203-205].

Specific comment (2)
Comment on. Why the Oxford Criteria were not acceptable. ..... I agree the Oxford criteria are not acceptable but a comment is warranted
Response.
Thanks. The Oxford criteria are inappropriate because they identify as cases of ME/CFS people whose illnesses are probably primarily psychiatric in nature. As a result, its use for epidemiological research tends to produce prevalence rates which are substantial overestimates. Therefore, we have clarified the 4th exclusion criterion as follows: 'Studies with an inappropriate case definition (e.g., CFS-like illness or other clinical criteria, such as the Oxford criteria due to lack of specificity)' [see, page 8, lines 146-147].

VERSION 2 – REVIEW

REVIEWER	Dr Abhijit Chaudhuri Queen's Hospital, Romford, United Kingdom
REVIEW RETURNED	03-Jul-2018

GENERAL COMMENTS	The revised protocol of review is acceptable with a defined selection criteria and time frame.

REVIEWER	Elizabeth R. Unger PhD, MD Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Diseases
REVIEW RETURNED	18-Jul-2018

GENERAL COMMENTS	No further comments.